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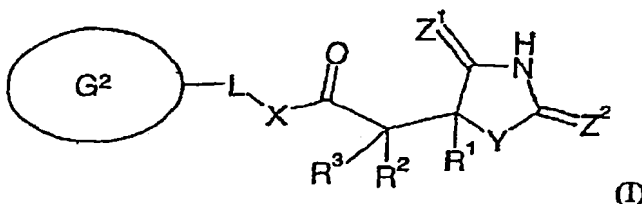
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(54) Title: 2,5-DIOXOIMIDAZOLIDIN-4-YL ACETAMIDES AND ANALOGUES AS INHIBITORS OF METALLOPRO-
TEINASE MMP12.



(I)

such as asthma and chronic obstructive pulmonary disease (COPD).

(57) Abstract: The invention provides compounds of
formula (I) in which L, X, Y, Z¹, Z², R¹, R², R³ and
G² have the meanings defined in the specification;
processes for their preparation; pharmaceutical
compositions containing them; a process for preparing
the pharmaceutical compositions; and their use in
therapy. The compounds of the invention are inhibitors
of metalloproteinase MMP12 and are among other things
useful for the treatment of obstructive airways diseases,

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2,5-DIOXOIMIDAZOLIDIN-4-YLACETAMIDES AND ANALOGUES AS INHIBITORS OF METALLOPROTEINASE MMP12.

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

5 Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMPs) such as the collagenases (MMP1, MMP8, MMP13), the
10 gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the
15 astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation
20 and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biological important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically
25 important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many diseases or conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these diseases or

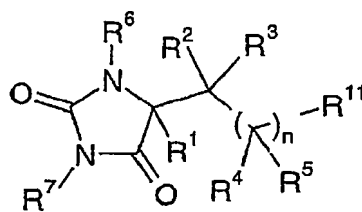
conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atherosclerosis; asthma; rhinitis; and chronic obstructive pulmonary diseases (COPD).

MMP12, also known as macrophage elastase or metalloelastase, was initially cloned in the mouse by Shapiro *et al* [1992, Journal of Biological Chemistry 267: 4664] and in man by the same group in 1995. MMP12 is preferentially expressed in activated macrophages, and has been shown to be secreted from alveolar macrophages from smokers [Shapiro *et al*, 1993, Journal of Biological Chemistry, 268: 23824] as well as in foam cells in atherosclerotic lesions [Matsumoto *et al*, 1998, Am J Pathol 153: 109]. A mouse model of COPD is based on challenge of mice with cigarette smoke for six months, two cigarettes a day six days a week. Wildtype mice developed pulmonary emphysema after this treatment. When MMP12 knock-out mice were tested in this model they developed no significant emphysema, strongly indicating that MMP12 is a key enzyme in the COPD pathogenesis. The role of MMPs such as MMP12 in COPD (emphysema and bronchitis) is discussed in Anderson and Shinagawa, 1999, Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs 1(1): 29-38. It was recently discovered that smoking increases macrophage infiltration and macrophage-derived MMP-12 expression

in human carotid artery plaques Kangavari [Matetzky S, Fishbein MC *et al.*, Circulation 102:(18), 36-39 Suppl. S, Oct 31, 2000].

A number of metalloproteinase inhibitors are known (see for example the reviews of MMP inhibitors by Beckett R.P. and Whittaker M., 1998, Exp. Opin. Ther. Patents, 8(3):259-282, and by Whittaker M. *et al.*, 1999, Chemical Reviews 99(9):2735-2776).

Published International Patent Application No. WO 02/096426 (Bristol- Myers Squibb Company) describes hydantoin derivatives of formula

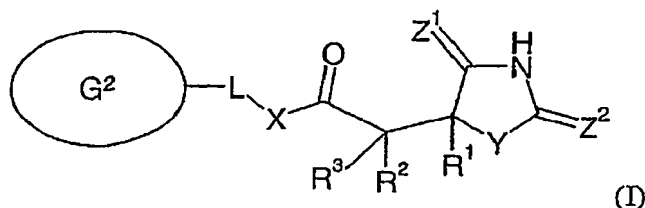


in which the substituents R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R¹¹ are broadly defined. The derivatives are said, in general terms, to act as inhibitors of metalloproteinases, in particular TACE, MMPs and/or aggrecanase, although no data demonstrating biological activity is included in the application.

We have now discovered a new class of compounds that are potent and selective MMP12 inhibitors and have desirable activity profiles, in particular they are highly selective inhibitors for MMP12 relative to, for example, MMP14, MMP19 and TACE.

In accordance with the present invention, there is therefore provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof

4



wherein

X represents an oxygen atom or a group NR^4 or CH_2 ;

Y represents NH or N-methyl;

5 Z^1 and Z^2 each independently represent an oxygen or sulphur atom, provided that at least one of Z^1 and Z^2 represents an oxygen atom;

Either R^1 represents hydrogen or a group selected from C_1 - C_6 alkyl and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, carboxyl, $-\text{NR}^5\text{R}^6$, $-\text{CONR}^7\text{R}^8$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylcarbonyl(oxy), $-\text{S}(\text{O})_m\text{C}_1$ - C_6 alkyl where m is 0, 1 or 2, C_1 - C_6 alkylsulphonylamino, C_1 - C_6 alkoxy carbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo ($=\text{O}$), carboxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 alkoxy carbonyl and C_1 - C_6 hydroxyalkyl,

R^2 represents hydrogen or C_1 - C_6 alkyl, and

R^3 represents hydrogen or C_1 - C_6 alkyl,

20 or

R^1 and R^2 together with the carbon atoms to which they are attached form a saturated 5- to 6-membered ring optionally comprising a ring heteroatom selected from nitrogen, oxygen and sulphur, and R^3 is as defined above,

or

R^2 and R^3 together with the carbon atom to which they are attached form a saturated 5- to 6-membered ring optionally comprising a ring heteroatom selected from nitrogen, oxygen and sulphur, and R^1 is as defined above;

R^4 represents hydrogen or C_1 - C_6 alkyl;

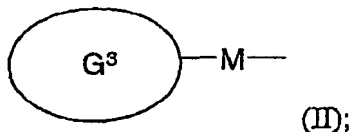
5 R^5 , R^6 , R^7 and R^8 each independently represent hydrogen or C_1 - C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy;

L represents $-CH_2C(O)-$ or $-C(O)CH_2-$, or

L represents a C_2 - C_6 alkyl or C_2 - C_6 alkynyl group optionally interrupted or terminated by at least one moiety selected from O, NH, S, SO, SO_2 and $C(O)$, or L
10 represents a C_3 - C_6 cycloalkyl, methyl- C_3 - C_6 cycloalkyl or C_3 - C_6 cycloalkylmethyl group, each of the recited groups being optionally substituted with at least one substituent selected from hydroxyl, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy and C_1 - C_4 haloalkoxy, or

L represents a C_3 - C_4 alkylene chain, the ends of which are attached to adjacent ring
15 carbon atoms in the 5- to 10-membered ring system of G^2 to form a ring;

G^2 represents a saturated or unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, nitro, C_1 - C_6 alkyl (optionally substituted by one or more of cyano, halogen, hydroxyl and methoxy), C_2 - C_6 alkenyl, C_1 - C_6 alkoxy (optionally substituted by
20 one or more halogen atoms), $-S(O)_n C_1$ - C_6 alkyl where n is 0, 1 or 2, C_1 - C_6 alkylcarbonyl(amino), C_1 - C_6 alkylcarbonyloxy, phenyl, benzyloxy, $-NR^9 R^{10}$ and a group of formula



25 R^9 and R^{10} each independently represent hydrogen or C_1 - C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy;

M represents a bond or $-O-$, $-S-$, $-C\equiv C-$, $-CH_2O-$ or $-OCH_2-$;

G^3 represents an unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, nitro, C_1 - C_6 alkyl (optionally substituted by one or more of cyano, halogen, hydroxyl and methoxy), C_2 - C_6 alkenyl, C_1 - C_6 alkoxy (optionally substituted by one or more halogen atoms), $-S(O)_tC_1$ - C_6 alkyl where t is 0, 1 or 2, C_1 - C_6 alkylcarbonyl(amino), C_1 - C_6 alkylcarbonyloxy, phenyl, benzyloxy and $-NR^{11}R^{12}$; and R^{11} and R^{12} each independently represent hydrogen or C_1 - C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy.

In the context of the present specification, unless otherwise stated, an alkyl, alkenyl or alkynyl substituent group or an alkyl moiety in a substituent group may be linear or branched. A haloalkyl or haloalkoxy substituent group will comprise at least one halogen atom, e.g. one, two, three or four halogen atoms. A hydroxyalkyl substituent may contain one or more hydroxyl groups but preferably contains one or two hydroxyl groups. When R^1 and R^2 , or R^2 and R^3 , form a ring, it should be understood that the ring may comprise up to one ring heteroatom only. In the definition of R^1 , it should be noted that each of the saturated or unsaturated 3- to 10-membered ring system and the saturated or unsaturated 5- to 6-membered ring may have alicyclic or aromatic properties. The same comment applies to the saturated or unsaturated 5- to 10-membered ring system in the definition of G^2 .

An unsaturated ring system will be partially or fully unsaturated. When L represents a C_2 - C_6 alkyl or C_2 - C_6 alkynyl group optionally interrupted or terminated by more than one moiety (e.g. two moieties) selected from O, NH, S, SO, SO_2 and C(O), it may in some instances be possible for the two moieties to be adjacent to one another but otherwise the moieties will need to be separated by one or more carbon atoms. For example, whilst it is acceptable for C(O) or SO_2 and NH to be adjacent to one another, combinations such as NH-NH, NH-O, O-O, O-SO, O- SO_2 , SO-SO, SO_2 - SO_2 and so on are undesirable. The person skilled in the art will know which moieties may be placed next to one another.

In an embodiment of the invention, X represents an oxygen atom or a group NR^4 where R^4 represents hydrogen or $\text{C}_1\text{-C}_6$, preferably $\text{C}_1\text{-C}_4$, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

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In another embodiment of the invention, X represents NH or N-methyl. In a further embodiment, X represents NH.

In one embodiment, Z^1 and Z^2 both represent an oxygen atom.

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In an embodiment of the invention, R^1 represents hydrogen or a group selected from $\text{C}_1\text{-C}_6$, preferably $\text{C}_1\text{-C}_4$, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each group being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, cyano, carboxyl, $-\text{NR}^5\text{R}^6$, $-\text{CONR}^7\text{R}^8$, $\text{C}_1\text{-C}_6$, preferably $\text{C}_1\text{-C}_4$, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), $\text{C}_1\text{-C}_6$, preferably $\text{C}_1\text{-C}_4$, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), $\text{C}_1\text{-C}_6$, preferably $\text{C}_1\text{-C}_4$, alkylcarbonyl(oxy) (e.g. methylcarbonyl(oxy), ethylcarbonyl(oxy), n-propylcarbonyl(oxy), isopropylcarbonyl(oxy), n-butylcarbonyl(oxy), n-pentylcarbonyl(oxy) or n-hexylcarbonyl(oxy)), $-\text{S}(\text{O})_m\text{C}_1\text{-C}_6$, preferably $\text{C}_1\text{-C}_4$, alkyl where m is 0, 1 or 2 (e.g. methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl or ethylsulphonyl), $\text{C}_1\text{-C}_6$, preferably $\text{C}_1\text{-C}_4$, alkylsulphonylamino (e.g. methylsulphonylamino, ethylsulphonylamino, n-propylsulphonylamino, isopropylsulphonylamino, n-butylsulphonylamino, n-pentylsulphonylamino or n-hexylsulphonylamino), $\text{C}_1\text{-C}_6$, preferably $\text{C}_1\text{-C}_4$, alkoxycarbonyl(amino) (e.g. methoxycarbonyl(amino), ethoxycarbonyl(amino), n-propoxycarbonyl(amino) or

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n-butoxycarbonyl(amino)), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, oxo, carboxyl, cyano, C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C₁-C₆, preferably C₁-C₄, alkoxy carbonyl (e.g. methoxycarbonyl or ethoxycarbonyl) and C₁-C₆, preferably C₁-C₄, hydroxyalkyl (e.g. -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH or -CH(OH)CH₃);
5 R² represents hydrogen or C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl); and
R³ represents hydrogen or C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

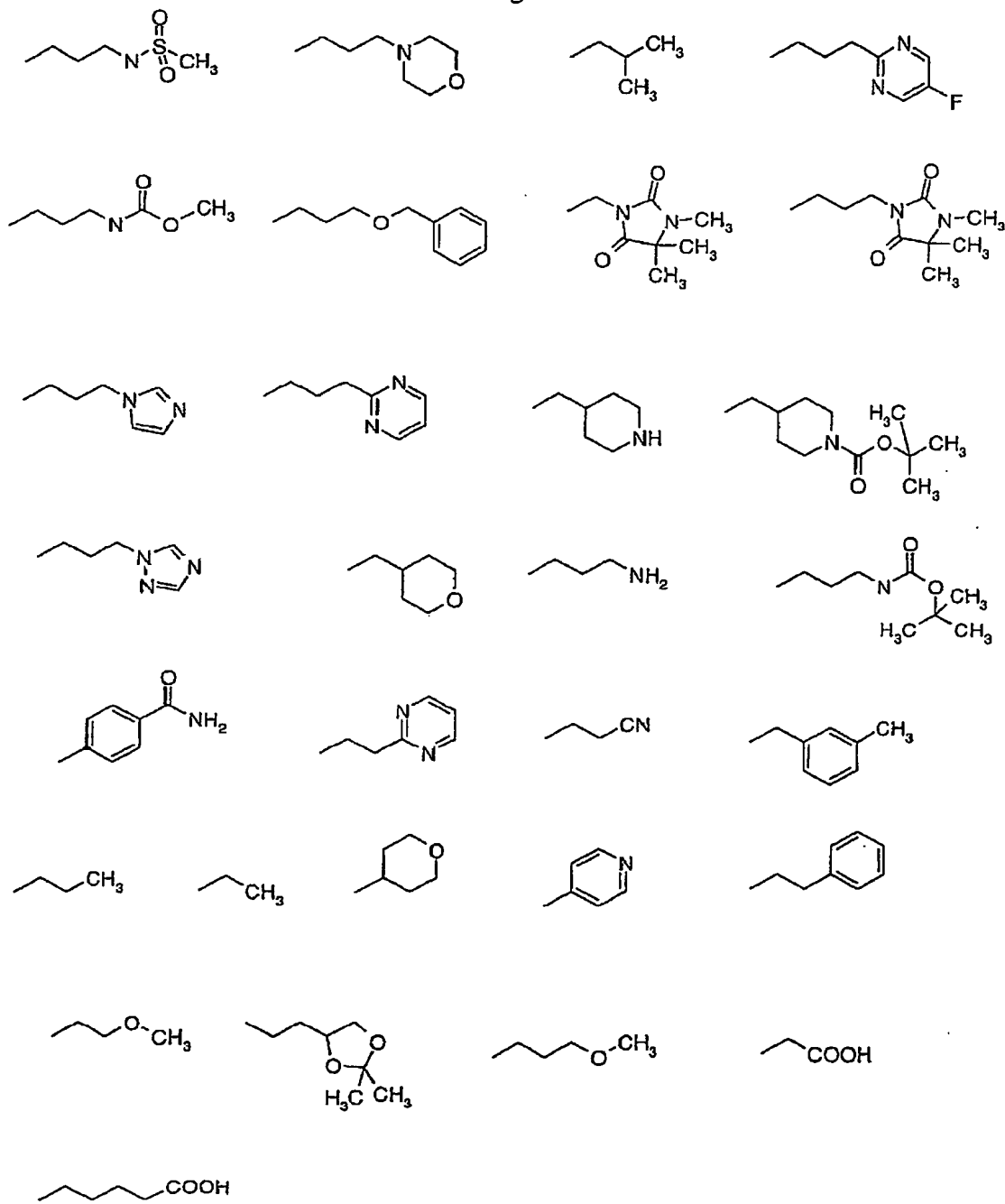
15 Examples of saturated or unsaturated 3- to 10-membered ring systems that may be used, which may be monocyclic or polycyclic (e.g. bicyclic) in which the two or more rings are fused, include one or more (in any combination) of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, cyclopentenyl, cyclohexenyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazabicyclo[2.2.1]hept-2-yl,
20 naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, quinolinyl, 2,3-dihydrobenzofuranyl, tetrahydropyranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, imidazolyl, pyrimidinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl. Preferred ring systems include phenyl, pyridinyl and tetrahydropyranyl.

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Examples of saturated or unsaturated 5- to 6-membered ring substituents in R¹ include cyclopentyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiomorpholinyl, pyrazolyl, pyrazinyl, pyridazinyl, thiazolidinyl, thienyl, isoxazolyl, pyrimidinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, imidazolyl,

triazolyl, tetrazolyl and pyridinyl. Preferred rings include morpholinyl, pyrimidinyl, phenyl, imidazolyl, piperidinyl, tetrahydropyranyl and triazolyl.

Particular values for R¹ include the following:



In another embodiment of the invention, R^1 represents hydrogen or a group selected from C_1 - C_4 alkyl and a saturated or unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each group being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen, hydroxyl, cyano, carboxyl, $-NR^5R^6$, $-CONR^7R^8$, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkylcarbonyl(oxy), $-S(O)_mC_1$ - C_4 alkyl where m is 0, 1 or 2, C_1 - C_4 alkylsulphonylamino, C_1 - C_4 alkoxycarbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen, hydroxyl, oxo, carboxyl, cyano, C_1 - C_4 alkyl C_1 - C_4 alkoxycarbonyl and C_1 - C_4 hydroxyalkyl;

R^2 represents hydrogen or C_1 - C_4 alkyl; and

R^3 represents hydrogen or C_1 - C_4 alkyl.

In still another embodiment, R^1 represents hydrogen or C_1 - C_4 alkyl, particularly methyl; R^2 represents hydrogen; and R^3 represents hydrogen.

Alternatively, R^1 and R^2 may together with the carbon atoms to which they are attached form a saturated 5- to 6-membered ring optionally comprising a ring heteroatom selected from nitrogen, oxygen and sulphur (e.g. cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, tetrahydrofuranyl or tetrahydrothiophenyl), and R^3 is as previously defined.

As a further alternative, R^2 and R^3 may together with the carbon atom to which they are attached form a saturated 5- to 6-membered ring optionally comprising a ring heteroatom selected from nitrogen, oxygen and sulphur (e.g. cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, tetrahydrofuranyl or tetrahydrothiophenyl), and R^1 is as previously defined.

R^5 , R^6 , R^7 and R^8 each independently represent hydrogen or C_1 - C_6 , preferably C_1 - C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine) and C_1 - C_6 , preferably C_1 - C_4 , alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

In an embodiment of the invention, R^5 , R^6 , R^7 and R^8 each independently represent hydrogen or C_1 - C_6 , preferably C_1 - C_4 , alkyl. In another embodiment, R^5 , R^6 , R^7 and R^8 each independently represent hydrogen.

L represents $-CH_2C(O)-$ or $-C(O)CH_2-$, or

L represents a C_2 - C_6 , preferably C_2 - C_4 , alkyl or C_2 - C_6 , preferably C_2 - C_4 , alkynyl group

optionally interrupted or terminated by at least one moiety (e.g. one or two moieties independently) selected from O, NH, S, SO, SO_2 and C(O) (for example, $-(CH_2)_2-$,

$-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-C\equiv C-$, $-CH_2-C\equiv C-$, $-C\equiv C-CH_2-$,

$-O-(CH_2)_3-NH-$, $-NH-(CH_2)_3-O-$, $-CH(CH_3)-$, $-(CH_2)_2-C(O)-$, $-C(O)-(CH_2)_2-$,

$-CH_2CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-(CH_2)_2-O-CH_2-$ or $-CH_2-O-(CH_2)_2$), or L represents

a C_3 - C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), methyl- C_3 - C_6 cycloalkyl (e.g. methylcyclopropyl) or C_3 - C_6 cycloalkylmethyl (e.g. cyclopropylmethyl)

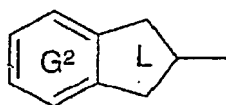
group, each of the recited groups being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine), C_1 - C_4 , preferably C_1 - C_2 , alkyl (e.g. methyl, ethyl,

n-propyl, isopropyl, n-butyl or t-butyl), C_1 - C_4 , preferably C_1 - C_2 , haloalkyl (e.g.

trifluoromethyl or pentafluoroethyl), C_1 - C_4 , preferably C_1 - C_2 , alkoxy (e.g. methoxy or ethoxy) and C_1 - C_4 , preferably C_1 - C_2 , haloalkoxy (e.g. trifluoromethoxy)

(such as $-\text{CH}_2\text{OCH}(\text{R})\text{CH}_2\text{NH}-$ or $-\text{NHCH}_2\text{CH}(\text{R})\text{OCH}_2-$ where R represents methyl, hydroxyl or methoxy, $-\text{CH}(\text{CH}_3)-\text{CH}(\text{OH})-$, $-\text{CH}(\text{OH})-\text{CH}(\text{CH}_3)-$, $-\text{CH}_2\text{CH}(\text{OH})-$, $-\text{CH}(\text{OH})\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{OCH}_3)-$ or $-\text{CH}(\text{OCH}_3)\text{CH}_2-$), or

L represents a C_3 - C_4 alkylene chain, the ends of which are attached to adjacent ring carbon atoms in the 5- to 10-membered ring system of G^2 to form a ring (for example, if G^2 represents an unsubstituted phenyl group and L represents a C_3 alkylene chain, G^2 and L together form a 2,3-dihydroinden-2-yl group having the structure:



In an embodiment of the invention, reading from left to right in formula (I),
 10 L represents $-\text{C}(\text{O})\text{CH}_2-$, or

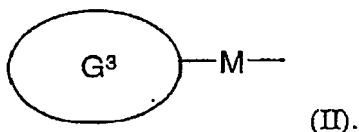
L represents C_2 - C_4 alkyl optionally interrupted or terminated by an oxygen atom, cyclopropyl or cyclopropylmethyl, each of which is optionally substituted with one or two substituents independently selected from hydroxyl, halogen, methyl, trifluoromethyl, methoxy and trifluoromethoxy, or

15 L represents a C_3 - C_4 alkylene chain, the ends of which are attached to adjacent ring carbon atoms in the 5- to 10-membered ring system of G^2 to form a ring.

In a further embodiment of the invention, L represents (reading from left to right in formula (I)) $-\text{C}(\text{O})\text{CH}_2-$, $-(\text{CH}_2)_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}(\text{OH})-\text{CH}(\text{CH}_3)-$,
 20 $-\text{CH}(\text{OH})\text{CH}_2-$, $-\text{CH}(\text{OCH}_3)\text{CH}_2-$, $-\text{CH}_2-\text{O}-(\text{CH}_2)_2$, cyclopropyl, cyclopropylmethyl, or
 L represents a C_3 alkylene chain, the ends of which are attached to adjacent ring carbon atoms in the 5- to 10-membered ring system of G^2 to form a ring.

G^2 represents a saturated or unsaturated 5- to 10-membered ring system which may
 25 comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with at least one substituent (e.g. one, two, three or four substituents

independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, cyano, nitro, C₁-C₆, preferably C₁-C₄, alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen such as chlorine, fluorine, bromine or iodine, hydroxyl and methoxy), C₂-C₆, preferably C₂-C₄, alkenyl (e.g. ethenyl, prop-1-enyl, prop-2-enyl, but-1-enyl, pent-1-enyl, hex-1-enyl or 2-methyl-pent-2-enyl), C₁-C₆, preferably C₁-C₄, alkoxy such as methoxy, ethoxy, n-propoxy or n-butoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine), -S(O)_nC₁-C₆, preferably C₁-C₄, alkyl where n is 0, 1 or 2 (e.g. methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl or ethylsulphonyl), C₁-C₆, preferably C₁-C₄, alkylcarbonyl(amino) (e.g. methylcarbonyl(amino), ethylcarbonyl(amino), n-propylcarbonyl(amino), isopropylcarbonyl(amino), n-butylcarbonyl(amino), n-pentylcarbonyl(amino) or n-hexylcarbonyl(amino)), C₁-C₆, preferably C₁-C₄, alkylcarbonyloxy (e.g. methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, isopropylcarbonyloxy, n-butylcarbonyloxy, n-pentylcarbonyloxy or n-hexylcarbonyloxy), phenyl, benzyloxy, -NR⁹R¹⁰ and a group of formula



Examples of saturated or unsaturated 5- to 10-membered ring systems that may be used in G², which may be monocyclic or polycyclic (e.g. bicyclic) in which the two or more rings are fused, include one or more (in any combination) of cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, cyclopentenyl, cyclohexenyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazabicyclo[2.2.1]hept-2-yl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, quinolinyl, 2,3-dihydrobenzofuranyl, tetrahydropyranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, imidazolyl, pyrimidinyl,

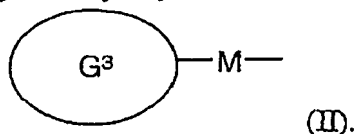
benzimidazolyl, triazolyl, tetrazolyl and pyridinyl. Preferred ring systems include phenyl, indolyl, thienyl and piperidinyl.

R^9 and R^{10} each independently represent hydrogen or C_1 - C_6 , preferably C_1 - C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine) and C_1 - C_6 , preferably C_1 - C_4 , alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

10

In an embodiment of the invention, G^2 represents a saturated or unsaturated 5- to 9-membered ring system which may comprise one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with one or two substituents independently selected from halogen, hydroxyl, cyano, nitro, C_1 - C_4 alkyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen such as chlorine, fluorine, bromine or iodine, hydroxyl and methoxy), C_2 - C_4 alkenyl, C_1 - C_4 alkoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine), $-S(O)_n C_1$ - C_4 alkyl where n is 0, 1 or 2, C_1 - C_4 alkylcarbonyl(amino), C_1 - C_4 alkylcarbonyloxy, phenyl, benzyloxy, $-NR^9 R^{10}$ and a group of formula

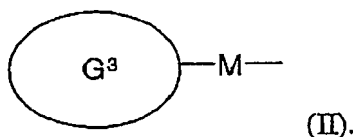
20



In another embodiment, G^2 represents a saturated or unsaturated 5- to 9-membered ring system which may comprise one ring heteroatom selected from nitrogen and sulphur (e.g. phenyl, indolyl, thienyl or piperidinyl), the ring system being optionally substituted with one or two substituents independently selected from halogen, C_1 - C_4 alkyl and a group of formula

25

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In an embodiment of the invention, M represents a bond, -O- or -C≡C-. In a further embodiment, M represents a bond.

5

G^3 represents an unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from

10 halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, cyano, nitro, C_1-C_6 , preferably C_1-C_4 , alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen such as chlorine, fluorine, bromine or iodine, hydroxyl and methoxy), C_2-C_6 , preferably C_2-C_4 , alkenyl (e.g.

15 ethenyl, prop-1-enyl, prop-2-enyl, but-1-enyl, pent-1-enyl, hex-1-enyl or 2-methylpent-2-enyl), C_1-C_6 , preferably C_1-C_4 , alkoxy such as methoxy, ethoxy, n-propoxy or n-butoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine), $-S(O)_t C_1-C_6$, preferably C_1-C_4 , alkyl where t is 0, 1 or 2 (e.g. methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl or

20 ethylsulphonyl), C_1-C_6 , preferably C_1-C_4 , alkylcarbonyl(amino) (e.g. methylcarbonyl(amino), ethylcarbonyl(amino), n-propylcarbonyl(amino), isopropylcarbonyl(amino), n-butylcarbonyl(amino), n-pentylcarbonyl(amino) or n-hexylcarbonyl(amino)), C_1-C_6 , preferably C_1-C_4 , alkylcarbonyloxy (e.g. methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, isopropylcarbonyloxy,

25 n-butylcarbonyloxy, n-pentylcarbonyloxy or n-hexylcarbonyloxy), phenyl, benzyloxy and $-NR^{11}R^{12}$.

Examples of unsaturated 5- to 10-membered ring systems that may be used in G^3 , which may be monocyclic or polycyclic (e.g. bicyclic) in which the two or more rings are fused, include one or more (in any combination) of cyclopentenyl, cyclohexenyl, phenyl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, quinoliny, 2,3-
 5 dihydrobenzofuranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, imidazolyl, pyrimidinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl. Preferred ring systems include phenyl, thienyl, naphthyl, benzofuranyl, benzothienyl, pyridinyl, pyrrolyl, furanyl, benzodioxolyl, quinoliny and 2,3-dihydrobenzofuranyl.

10 R^{11} and R^{12} each independently represent hydrogen or C_1-C_6 , preferably C_1-C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or
 15 iodine) and C_1-C_6 , preferably C_1-C_4 , alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

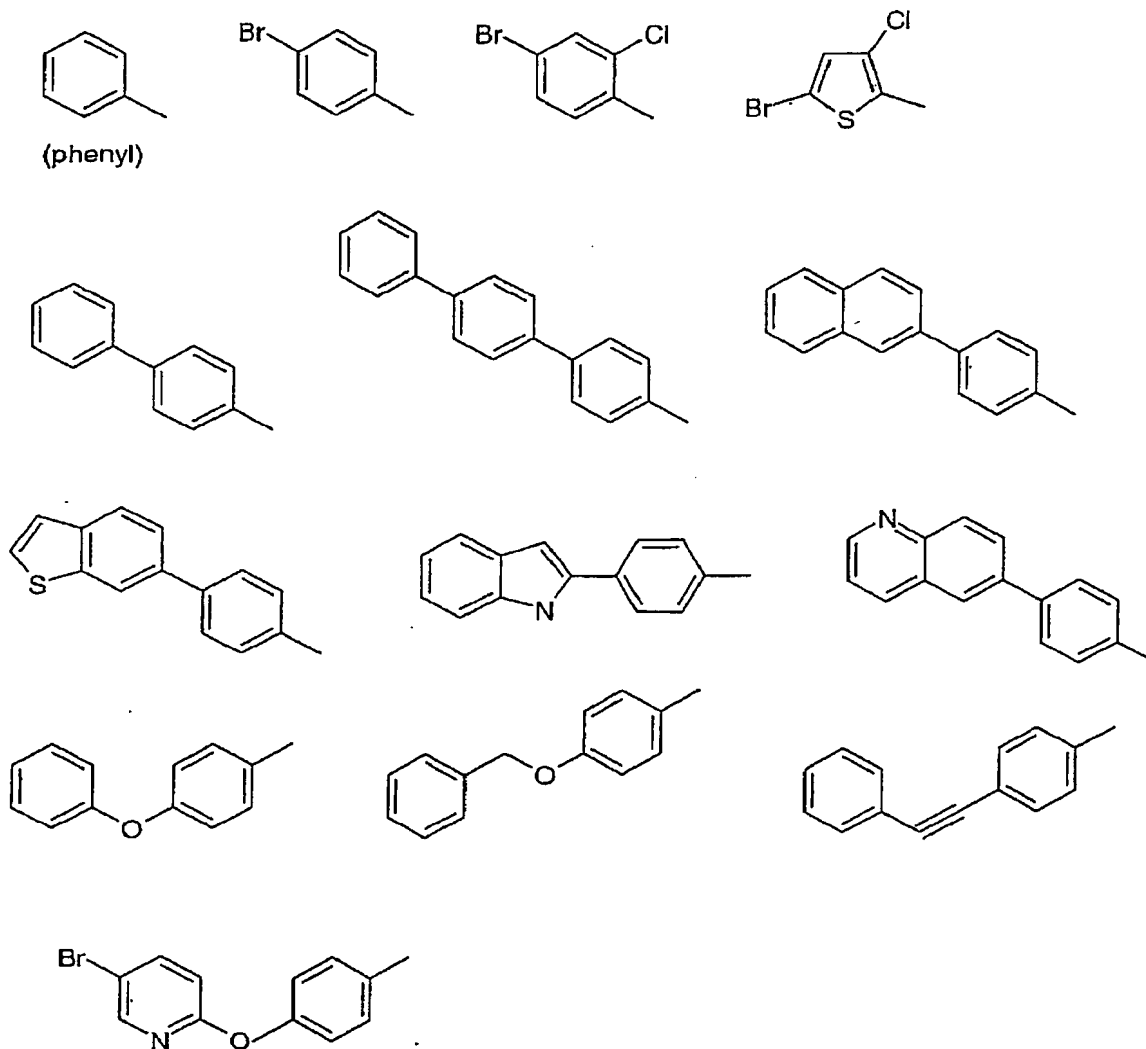
In one embodiment, G^3 represents an unsaturated 5- to 10-membered ring system which may comprise one or two ring heteroatoms independently selected from nitrogen, oxygen
 20 and sulphur (e.g. phenyl, thienyl, naphthyl, benzofuranyl, benzothienyl, pyridinyl, pyrrolyl, furanyl, benzodioxolyl, quinoliny and 2,3-dihydrobenzofuranyl), the ring system being optionally substituted with one or two substituents independently selected from halogen, hydroxyl, cyano, nitro, C_1-C_4 alkyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen such as chlorine,
 25 fluorine, bromine or iodine, hydroxyl and methoxy), C_2-C_4 alkenyl, C_1-C_4 alkoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine), $-S(O)_t C_1-C_4$ alkyl where t is 0, 1 or 2, C_1-C_4 alkylcarbonyl(amino), C_1-C_4 alkylcarbonyloxy, phenyl, benzyloxy and $-NR^{11}R^{12}$

In another embodiment, G^3 represents an unsaturated 5- to 10-membered ring system which may comprise one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur (e.g. phenyl, thienyl, naphthyl, benzofuranyl, benzothienyl, pyridinyl, pyrrolyl, furanyl, benzodioxolyl, quinolinyl and 2,3-dihydrobenzofuranyl), the ring system being optionally substituted with one or two substituents independently selected from halogen, cyano, nitro, C_1 - C_4 alkyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano and halogen), C_1 - C_4 alkoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms), C_1 - C_4 alkylthio, C_1 - C_4 alkylcarbonyl(amino), phenyl and benzyloxy.

In still another embodiment, G^3 represents an unsaturated 5- to 10-membered ring system which may comprise one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur (e.g. phenyl, thienyl, naphthyl, benzofuranyl, benzothienyl, pyridinyl, pyrrolyl, furanyl, benzodioxolyl, quinolinyl and 2,3-dihydrobenzofuranyl), the ring system being optionally substituted with one or two substituents independently selected from fluorine, chlorine, cyano, nitro, methyl, cyanomethyl, trifluoromethyl, methoxy, trifluoromethoxy, methylthio, methylcarbonyl (acetyl), methylcarbonylamino (acetylamino), phenyl and benzyloxy.

Particular values for G^2 include the following:

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In an embodiment of the invention:

X represents -NH- or $\text{-N(CH}_3\text{)-}$;

Y represents NH;

Z^1 and Z^2 both represent an oxygen atom;

R^1 represents hydrogen or methyl;

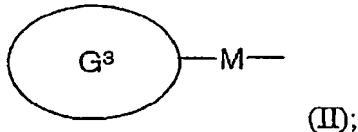
R^2 represents hydrogen;

R^3 represents hydrogen;

L represents -C(O)CH₂-, -(CH₂)₂-, -CH(CH₃)-, -CH(CH₃)CH₂-,
-CH(OH)-CH(CH₃)-, -CH(OH)CH₂-, -CH(OCH₃)CH₂-, -CH₂-O-(CH₂)₂, cyclopropyl,
cyclopropylmethyl, or

L represents a C₃ alkylene chain, the ends of which are attached to adjacent ring
5 carbon atoms in the 5- to 9-membered ring system of G² to form a ring;

G² represents a saturated or unsaturated 5- to 9-membered ring system
which may comprise one ring heteroatom selected from nitrogen and sulphur, the ring
system being optionally substituted with one or two substituents independently selected
from halogen, C₁-C₄ alkyl and a group of formula



10

M represents a bond, -O- or -C≡C-; and

G³ represents an unsaturated 5- to 10-membered ring system which may comprise one
or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the
ring system being optionally substituted with one or two substituents independently
15 selected from fluorine, chlorine, cyano, nitro, methyl, cyanomethyl, trifluoromethyl,
methoxy, trifluoromethoxy, methylthio, methylcarbonyl, methylcarbonylamino, phenyl
and benzyloxy.

Examples of compounds of the invention include:

- 20 2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-fluoro-biphenyl-4-yl)-ethyl]-acetamide,
N-[2-(4'-Cyano-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-phenyl-cyclopropyl)-acetamide,
N-[2-(4-Chlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
N-(2-Biphenyl-4-yl-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
25 2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(7-methyl-1H-indol-3-yl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-phenoxyphenyl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-fluorophenyl)ethyl]-acetamide,

- N*-[2-(4-Bromophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
N-[2-(2,4-Dichlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
N-[2-(3'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
N-[2-(4'-Benzyloxy-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
5 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-thiophen-3-yl-phenyl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-thiophen-2-yl-phenyl)ethyl]-acetamide,
N-[2-(4'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-methylsulfanyl-biphenyl-4-yl)ethyl]-
acetamide,
10 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-nitro-biphenyl-4-yl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-methyl-biphenyl-4-yl)ethyl]-acetamide,
N-[2-(3'-Acetylamino-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-naphthalen-2-yl-phenyl)ethyl]-acetamide,
N-[2-(3',5'-Dichloro-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
15 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methyl-biphenyl-4-yl)ethyl]-acetamide,
N-[2-(4-Benzofuran-2-yl-phenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methoxy-biphenyl-4-yl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-[1,1';4',1'']terphenyl-4-yl)ethyl)-acetamide,
N-[2-(4'-Acetyl-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
20 *N*-[2-(4-Benzo[b]thiophen-2-yl-phenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-
acetamide,
N-[2-(4'-Cyanomethyl-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-pyridin-3-yl-phenyl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-(1H-pyrrol-2-yl)phenyl)ethyl]-acetamide,
25 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-furan-3-yl-phenyl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-furan-2-yl-phenyl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-thiophen-2-yl-ethyl)-acetamide,
N-[2-(4-tert-Butylphenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
N-[2-(4-Chlorophenyl)-1-methylethyl]-2-(2,5-dioxoimidazolidin-4-yl)acetamide,

N-{[1-(4-Chlorophenyl)cyclopropyl]methyl}-2-(2,5-dioxoimidazolidin-4-yl)acetamide,

N-2,3-Dihydro-1H-inden-2-yl-2-(2,5-dioxoimidazolidin-4-yl)acetamide,

N-[2-(4-Chlorophenyl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide,

5 *N*-[2-(4-Chlorophenyl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide,

N-[2-(4'-Cyano-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide,

N-[2-(4'-Fluoro-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide,

10 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-fluoro-1,1'-biphenyl-4-yl)propyl]-acetamide,

N-[(1*S*,2*R*)-2-(4'-Methoxybiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[(1*S*,2*R*)-2-(4'-Cyanobiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

15 *N*-[(1*S*,2*R*)-2-(4'-Acetylbiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{[(1*S*,2*R*)-2-[4'-(Acetylamino)biphenyl-4-yl]cyclopropyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Cyanobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

20 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methoxybiphenyl-4-yl)ethyl]-acetamide,

N-[2-(4'-Cyano-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-methyl-*N*-(2-phenylethyl)-acetamide,

25 *N*-[1-(4-Chlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-acetamide,

N-{2-[4-(1,3-Benzodioxol-5-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methoxybiphenyl-4-yl)propyl]-acetamide,

N-{2-[3'-(Acetylamino)biphenyl-4-yl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(3'-Acetylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Acetylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

5 *N*-{2-[4-(1-Benzothien-2-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(3'-Cyanobiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Cyanobiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

10 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-fluoro-3'-methylbiphenyl-4-yl)propyl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[3'-(methylthio)biphenyl-4-yl]propyl}-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[4-(6-methoxypyridin-3-yl)phenyl]propyl}-acetamide,

15 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-methoxy-3'-methylbiphenyl-4-yl)propyl]-acetamide,

N-{2-[4-(2,3-Dihydro-1-benzofuran-5-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

20 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[3'-(trifluoromethoxy)biphenyl-4-yl]propyl}-acetamide,

N-[2-(3',4'-Dimethoxybiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-quinolin-3-ylphenyl)propyl]-acetamide,

25 *N*-[2-(4'-Cyano-3'-methylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(1,3-Benzodioxol-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(3-methoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

N-{5-[3-(Acetylamino)phenyl]-2,3-dihydro-1H-inden-2-yl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

5 *N*-[5-(4-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(1-Benzothien-2-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

10 *N*-[5-(4-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(4-fluoro-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

15 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-[3-(methylthio)phenyl]-2,3-dihydro-1H-inden-2-yl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(6-methoxypyridin-3-yl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(4-methoxy-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

20 *N*-[5-(2,3-Dihydro-1-benzofuran-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)acetamide,

N-[5-(3,4-Dimethoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

25 *N*-[2-(4'-Fluorobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{2-[4-(1,3-Benzodioxol-5-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(3'-Methoxybiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{2-[4-(1-Benzothien-2-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

5 *N*-[2-(3'-Cyanobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Fluoro-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

10 2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-{2-[3'-(methylthio)biphenyl-4-yl]propyl}-acetamide,

N-{2-[4-(6-Methoxypyridin-3-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Methoxy-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

15 *N*-{2-[4-(2,3-Dihydro-1-benzofuran-5-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-{2-[3'-(trifluoromethoxy)biphenyl-4-yl]propyl}-acetamide,

20 *N*-[2-(3',4'-Dimethoxybiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-[2-(4-quinolin-3-ylphenyl)propyl]-acetamide,

N-[5-(4-Fluorophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

25 *N*-[5-(1,3-Benzodioxol-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Methoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{5-[3-(Acetylamino)phenyl]-2,3-dihydro-1H-inden-2-yl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

5 *N*-[5-(4-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(1-Benzothien-2-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

10 *N*-[5-(3-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Fluoro-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

15 2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-{5-[3-(methylthio)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide,

N-[5-(6-Methoxypyridin-3-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

20 *N*-[5-(4-Methoxy-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(2,3-Dihydro-1-benzofuran-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-{5-[3-(trifluoromethoxy)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide,

25 *N*-[5-(3,4-Dimethoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Cyano-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-{4-[4 (trifluoromethyl)phenoxy]phenyl}ethyl)-
acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-[4-(4-methoxyphenoxy)phenyl]ethyl)-
acetamide,

5 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-{4-[4-(trifluoromethoxy)phenoxy]phenyl}ethyl)-
acetamide,

N-(2-[4-(4-Chlorophenoxy)phenyl]ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-(2-[4-(4-Acetylphenoxy)phenyl]ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-[4-(pyridin-3-yloxy)phenyl]ethyl)-acetamide,

10 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-{4-[(6-methoxypyridin-3-yl)oxy]phenyl}ethyl)-
acetamide,

N-(2-[4-(4-Cyanophenoxy)phenyl]ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-[4-(4-methylphenoxy)phenyl]ethyl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-[4-(4-fluorophenoxy)phenyl]ethyl)-acetamide,

15 *N*-(2-Biphenyl-4-yl-2-hydroxy-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-(2-(1,1'-Biphenyl-4-yl)-2-methoxyethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-(2-(1,1'-Biphenyl-4-yl)-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-*N*-methylacetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-(4-phenylethynyl-piperidin-1-yl)ethyl)-
acetamide,

20 *N*-(2-[(4-Bromobenzyl)oxy]ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(1,1'-Biphenyl-4-yl)-2-oxoethyl (2,5-dioxoimidazolidin-4-yl)acetate,

and pharmaceutically acceptable salts and solvates thereof.

It will be appreciated that the particular substituents and number of substituents in the
25 compounds of the invention are selected so as to avoid sterically undesirable combinations.

Each exemplified compound represents a particular and independent aspect of the
invention.

It will be appreciated that the compounds according to the invention may contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres (chiral centres) in compounds according to the invention can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof. Racemates may be separated into individual optically active forms using known procedures (cf. Advanced Organic Chemistry: 3rd Edition: author J March, p104-107) including for example the formation of diastereomeric derivatives having convenient optically active auxiliary species followed by separation and then cleavage of the auxiliary species.

Where optically active centres exist in the compounds of the invention, we disclose all individual optically active forms and combinations of these as individual specific embodiments of the invention, as well as their corresponding racemates.

Where tautomers exist in the compounds of the invention, we disclose all individual tautomeric forms and combinations of these as individual specific embodiments of the invention.

The compounds of the invention may be provided as pharmaceutically acceptable salts or solvates. These include acid addition salts such as hydrochloride, hydrobromide, citrate, tosylate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine. Examples of solvates include hydrates.

The compounds of formula (I) have activity as pharmaceuticals. As previously outlined the compounds of the invention are metalloproteinase inhibitors, in particular they are inhibitors of MMP12 and may be used in the treatment of diseases or conditions mediated

by MMP12 such as asthma, rhinitis, chronic obstructive pulmonary diseases (COPD), arthritis (such as rheumatoid arthritis and osteoarthritis), atherosclerosis and restenosis, cancer, invasion and metastasis, diseases involving tissue destruction, loosening of hip joint replacements, periodontal disease, fibrotic disease, infarction and heart disease, liver
5 and renal fibrosis, endometriosis, diseases related to the weakening of the extracellular matrix, heart failure, aortic aneurysms, CNS related diseases such as Alzheimer's disease and Multiple Sclerosis (MS), and hematological disorders.

The compounds of the invention show a favourable selectivity profile. Whilst we do not
10 wish to be bound by theoretical considerations, the compounds of the invention are believed to show selective inhibition for any one of the above indications relative to any MMP1 inhibitory activity, by way of non-limiting example they may show 100-1000 fold selectivity over any MMP1 inhibitory activity.

15 Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a
20 pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and
25 "therapeutically" should be construed accordingly.

The invention further provides a method of treating a disease or condition mediated by MMP12 which comprises administering to a patient a therapeutically effective amount of a

compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined.

The invention also provides a method of treating an obstructive airways disease (e.g. asthma or COPD) which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I)/salt/solvate (active ingredient) may be in the range from 0.001 mg/kg to 75 mg/kg, in particular from 0.5 mg/kg to 30 mg/kg. This daily dose may be given in divided doses as necessary. Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as

hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical
5 composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

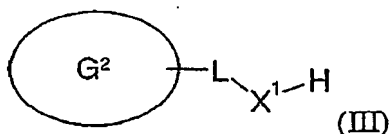
The pharmaceutical compositions of this invention may be administered in standard
10 manner for the disease or condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or
15 aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially)
20 with, one or more pharmacological agents of value in treating one or more diseases or conditions referred to hereinabove such as "Symbicort" (trade mark) product.

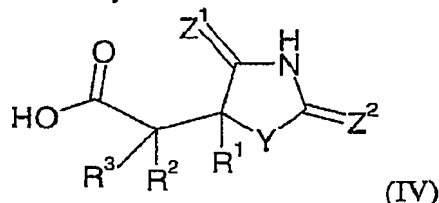
Preparation of the compounds of the invention

The present invention further provides a process for the preparation of a compound of
25 formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined above which comprises,

(a) when X represents an oxygen atom or a group NR^4 , reacting a compound of formula

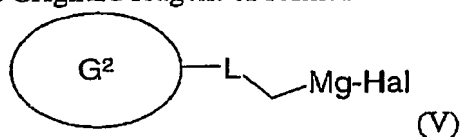


wherein X^1 represents an oxygen atom or a group NR^4 and L , G^2 and R^4 are as defined in formula (I), with an activated carboxylic acid of formula



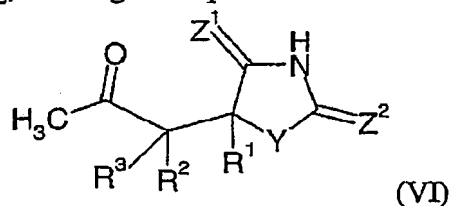
5 wherein Y , Z^1 , Z^2 , R^1 , R^2 and R^3 are as defined in formula (I); or

(b) when X represents CH_2 , reacting an activated carboxylic acid of formula (IV) as defined in (a) above with methoxymethylamine or a salt thereof (e.g. hydrochloride salt) followed by reaction with a Grignard reagent of formula

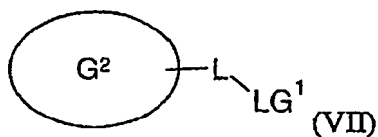


10 wherein Hal represents a halogen atom such as chlorine or bromine and L and G^2 are as defined in formula (I); or

(c) when X represents CH_2 , reacting a compound of formula



15 wherein Y , Z^1 , Z^2 , R^1 , R^2 and R^3 are as defined in formula (I), with a compound of formula



wherein LG^1 represents a leaving group such as halogen or sulphonate (e.g. methylsulphonate or toluenesulphonate) and L and G^2 are as defined in formula (I), in the presence of a strong base (e.g. sodium hydride or lithium diisopropylamide);

and optionally after (a), (b) or (c) forming a pharmaceutically acceptable salt or solvate.

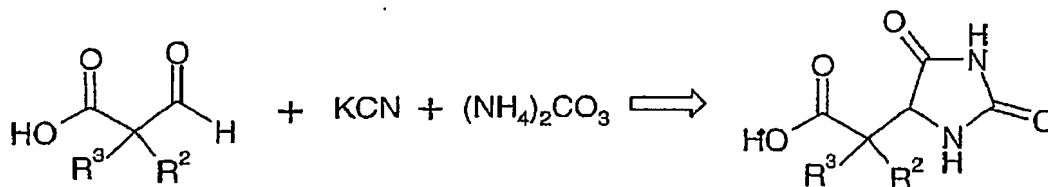
In process (a), the reaction between the compounds of formulae (III) and (IV) represents a simple amide or ester coupling well known to those skilled in the art. The carboxylic acid of formula (IV) must be activated in some way, for example as the acid halide, anhydride, acyl urea or acyl derivative of N-hydroxysuccinimide. For a general description of the preparation of amides and esters see, for example, Carey, F.A. and Sundberg, J., Advanced Organic Chemistry, 3rd Edition, pp 144-152, 1990.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of the invention may involve, at various stages, the addition and removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

Compounds of formulae (III), (IV), (V), (VI) and (VII) are either commercially available, are known in the literature or may be prepared using known techniques.

For example, compounds of formula (IV) in which R^1 represents a hydrogen atom, Y represents NH and Z^1 and Z^2 both represent oxygen may be prepared according to the reaction scheme below:



Intermediate 1

Alternatively, compounds of formula (IV) in which R^1 represents a hydrogen atom, Y represents NH, Z^1 represents sulphur and Z^2 represent oxygen may be prepared by reacting
 5 Intermediate 1 above with thiocarbamic acid ($\text{H}_2\text{N}-\text{C}(\text{S})-\text{OH}$) and sodium cyanide in the presence of a solvent mixture of ethanol and water, e.g. as described in *J. Chem. Soc.*, 1959, page 396.

Other methods are available for preparing compounds of formula (IV). For example, a
 10 wide range of α -amino acids are useful as synthons to dioxo-imidazolidines and oxo-thioxo-imidazolidines. It is well known that salts of cyanic acid, urea, or thiocyanic acid together with an ammonium salt react with α -amino acids to form these heterocycles (Anteunis, M.J.O.; Spiessens, L.; Witte, M. De; Callens, R.; Reyniers, *Bull. Soc. Chim.*
 15 *Belg.*, EN, 96, 6, 1987, 459-466; Dakin; *Am. Chem. J.*, 44, 1910, 49; Haurowitz et al., *J. Biol. Chem.*, 224, 1957).

Several suitable dioxo-imidazolidine and oxo-thioxo-imidazolidine acids are commercially available or are described in the literature as indicated below (unless otherwise stated, the
 20 numbers in brackets are CAS registry numbers):

(2,5-Dioxo-imidazolidin-4-yl)-acetic acid (5427-26-9, 26184-52-1, 26184-53-2, 67337-71-7);

(3-Methyl-2,5-dioxo-imidazolidin-4-yl)-acetic acid (26972-46-3);

5-Oxo-2-thioxo-imidazolidin-4-yl)-acetic acid (41679-36-1, 61160-00-7);

25 (2,5-Dioxo-4-phenyl-imidazolidin-4-yl)-acetic acid (62985-01-7);

(4-Methyl-2,5-dioxo-imidazolidin-4-yl)-acetic acid (*beilstein registry number 145446*);

4-Imidazolidineacetic acid, 4-(hydroxymethyl)-2,5-dioxo-, (4R)- (9CI) (391870-39-6);

5 4-Imidazolidineacetic acid, 4-(4-chlorophenyl)-2,5-dioxo- (9CI) (250352-11-5);

4-Imidazolidineacetic acid, α -methyl-2,5-dioxo- (9CI) (184681-52-5);

1,3-Diazaspiro[4.4]nonane-6-carboxylic acid, 2,4-dioxo-, cis- (9CI) (147676-21-9);

1,3-Diazaspiro[4.5]decane-6-carboxylic acid, 2,4-dioxo- (7CI, 8CI) (947-10-4);

1,3-Diazaspiro[4.4]nonane-6-carboxylic acid, 2-oxo-4-thioxo- (9CI) (197315-95-0);

10 4-Imidazolidineacetic acid, 5-oxo-2-thioxo- (9CI) (41679-36-1);

4,4-Imidazolidinediacetic acid, 2,5-dioxo- (8CI, 9CI) (5624-17-9); and

4-Imidazolidineacetic acid, 4-hydroxy-2,5-dioxo- (9CI) (78703-76-1).

The present invention will now be further explained by reference to the following
15 illustrative examples.

General procedures

¹HNMR and ¹³CNMR were recorded on a Varian ^{unity} Inova 400 MHz or a Varian Mercury-VX 300 MHz instrument. The central peaks of chloroform-*d* (δ_H 7.27ppm),
20 dimethylsulfoxide-*d*₆ (δ_H 2.50 ppm) or methanol-*d*₄ (δ_H 3.31 ppm) were used as internal references. Low-resolution mass spectra were obtained on an Agilent 100 LC-MS system equipped with an APCI ionisation chamber. Column chromatography was carried out using silica gel (0.063-0.2 mm) (Merck). Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were laboratory grade and
25 used as received.

Abbreviations:

NMP: 1-methyl-2-pyrrolidinone

TFA: trifluoroacetic acid

HOBT: 1-hydroxybenzotriazole

PdCl₂ (dppf): bis(diphenylphosphino)ferrocene-palladium(II)chloride dichloromethane complex

THF: tetrahydrofuran

BOC: *tert*-butoxycarbonyl

5 EtOH: ethanol

EtOAc: ethyl acetate

TLC: thin layer chromatography

DMSO: dimethyl sulphoxide

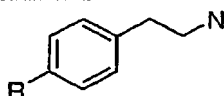
PEG: polyethylene glycol

10

Examples

A. General procedure for preparation of 2-(2,5-Dioxo-imidazolidin-4-yl)-acetamides

15 I. Preparation of non-commercial amines



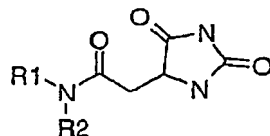
2-(4-Bromo-phenyl)-ethylamine (2mmol, 400mg) was dissolved in 4mL THF (dry, mol sieves) and di-*tert*-butyl dicarbonate (1.2eq 2.4mmol 520mg) was added slowly.

The reaction mixture was stirred in room temperature for 1 hour before it was diluted with
20 100mL ethyl acetate and washed with 100mL sat. NaHCO₃/aq. The organic phase was dried over Na₂SO₄, filtrated and evaporated to dryness. The BOC-protected amine was dissolved in a mixture of 10mL toluene, 2.5mL ethanol and 2.5mL 2M Na₂CO₃/aq. PdCl₂(dppf) (0.03eq, 50mg) was added together with a corresponding boronic acid (1.05eq, 2.1mmol). The solution was degassed with nitrogen and the vessel was sealed
25 before it was stirred overnight at 80°C. The reaction mixture was diluted with 50mL toluene and 50mL water. After mixing, the organic layer was transferred directly on to a silica column and purified by chromatography (toluene- ethylacetate). To remove the protecting group the compound was stirred in a mixture of 5mL conc. HCl in 10mL THF

for 30 min. The solution was neutralised with 1M NaOH/aq and extracted with dichloromethane (2x). The combined organic layers was dried over Na₂SO₄, filtrated and evaporated to dryness. The amines were used in the amide synthesis without any further purification.

5

II. Coupling of amines to 5 hydantoin acetic acid:- amide synthesis



600μL of a 0.15M solution in NMP of 5-hydantoin acetic acid was mixed with 98mg of polystyrene-bound carbodiimide resin (loading 1.28mmol/g). 340μL of a 0.3M solution of HOBT in NMP was added to the mixture and vortexed for 10 minutes before 200μL of a 0.3M solution in NMP of the corresponding amine was added. The reaction mixtures were vortexed overnight at room temperature in sealed vessels. Resin was removed by filtration and the solution was evaporated to dryness. The products were purified on semiprep-HPLC C₁₈-column (H₂O:CH₃CN, 0.1% TFA buffer, gradient 10% to 95% CH₃CN, 10 min).

15

The following 2-(2,5-Dioxo-imidazolidin-4-yl)-acetamides were prepared according to the general procedure A outlined above.

Example 1

20 **2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-fluoro-biphenyl-4-yl)-ethyl]-acetamide**
¹H NMR (400MHz, DMSO-d₆): δ 10.56 (1H, s); 8.07 (1H, t); 7.71-.7.65 (2H, m); 7.59-.7.55 (2H, m); 7.32-.7.24 (4H, m); 4.23-4.19 (1H, m); 3.35-3.26 (2H, m); 2.75 (2H, t) 2.56-2.37(2H, m)
 APCI-MS m/z: 356.4 [MH⁺]

25

Example 2

N-[2-(4'-Cyano-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

¹H NMR (400MHz,DMSO-d₆): δ 10.56 (1H, s); 8.07 (1H, t); 7.92-.7.84 (4H, m); 7.79 (1H, s); 7.69 (2H, d); 7.35 (2H, d); 4.21(1H, t); 3.37-3.27 (2H, m); 2.78 (2H, t) 2.57-2.36(2H, m)

APCI-MS m/z: 363.4 [MH⁺]

5

Example 3

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-phenyl-cyclopropyl)-acetamide

APCI-MS m/z: 274.3 [MH⁺]

10 Example 4

N-[2-(4-Chlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 296.3 [MH⁺]

Example 5

15 N-(2-Biphenyl-4-yl-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 338.4 [MH⁺]

Example 6

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(7-methyl-1H-indol-3-yl)ethyl]-acetamide

20 APCI-MS m/z: 315.3 [MH⁺]

Example 7

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-phenoxyphenyl)ethyl]-acetamide

APCI-MS m/z: 354.4 [MH⁺]

25

Example 8

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-fluorophenyl)ethyl]-acetamide

APCI-MS m/z: 280.3 [MH⁺]

Example 9

N-[2-(4-Bromophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 340.3 ; 342.3 [MH⁺]

5 **Example 10**

N-[2-(2,4-Dichlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 330.3 ; 332.3 [MH⁺]

Example 11

10 N-[2-(3'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 372.4 [MH⁺]

Example 12

N-[2-(4'-Benzyloxy-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

15 APCI-MS m/z: 444.5 [MH⁺]

Example 13

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-thiophen-3-yl-phenyl)ethyl]-acetamide

APCI-MS m/z: 344.3 [MH⁺]

20

Example 14

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-thiophen-2-yl-phenyl)ethyl]-acetamide

APCI-MS m/z: 344.3 [MH⁺]

25 **Example 15**

N-[2-(4'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 372.3 [MH⁺]

Example 16

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-methylsulfanyl-biphenyl-4-yl)ethyl]-acetamide

APCI-MS m/z: 384.4 [MH⁺]

5

Example 17

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(3'-nitro-biphenyl-4-yl)ethyl]-acetamide

APCI-MS m/z: 383.4 [MH⁺]

10 **Example 18**

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-methyl-biphenyl-4-yl)ethyl]-acetamide

APCI-MS m/z: 352.4 [MH⁺]

Example 1915

N-[2-(3'-Acetylamino-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 395.4 [MH⁺]

Example 20

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-naphthalen-2-yl-phenyl)ethyl]-acetamide

20

APCI-MS m/z: 388.4 [MH⁺]

Example 21

N-[2-(3',5'-Dichloro-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 406.3 ; 408.4 [MH⁺]

25

Example 22

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(3'-methyl-biphenyl-4-yl)ethyl]-acetamide

APCI-MS m/z: 352.4 [MH⁺]

Example 23

N-[2-(4-Benzofuran-2-yl-phenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 378.4 [MH⁺]

5 **Example 24**

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(3'-methoxy-biphenyl-4-yl)ethyl]-acetamide

APCI-MS m/z: 368.3 [MH⁺]

Example 25

10 2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-[1,1';4',1'']terphenyl-4-ylethyl)-acetamide

APCI-MS m/z: 414.4 [MH⁺]

Example 26

N-[2-(4'-Acetyl-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

15 APCI-MS m/z: 380.4 [MH⁺]

Example 27

N-[2-(4-Benzo[b]thiophen-2-yl-phenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

20 APCI-MS m/z: 394.4 [MH⁺]

Example 28

N-[2-(4'-Cyanomethyl-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 377.4 [MH⁺]

25

Example 29

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-pyridin-3-yl-phenyl)ethyl]-acetamide

APCI-MS m/z: 339.4 [MH⁺]

Example 30

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(1H-pyrrol-2-yl)phenyl]ethyl}-acetamide

APCI-MS m/z: 327.4 [MH⁺]

5 **Example 31**

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-furan-3-yl-phenyl)ethyl]-acetamide

APCI-MS m/z: 328.4 [MH⁺]

Example 3210

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-furan-2-yl-phenyl)ethyl]-acetamide

APCI-MS m/z: 328.4 [MH⁺]

Example 33

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-thiophen-2-yl-ethyl)-acetamide

15

APCI-MS m/z: 268.3 [MH⁺]

Example 34

N-[2-(4-tert-Butylphenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 318.4 [MH⁺]

20

Example 35

N-[2-(4-Chlorophenyl)-1-methylethyl]-2-(2,5-dioxoimidazolidin-4-yl)acetamide

¹H NMR (400MHz, DMSO-d₆): δ 10.55 (1H, d); 7.88 (1H, dd); 7.76 (1H, d); 7.33-7.31 (2H, m); 7.21-7.19 (2H, m); 4.19-4.16 (1H, m); 3.94-3.88 (1H, m); 2.77-2.32 (4H, m); 0.99 (3H, dd)

25

APCI-MS m/z: 310.3 [MH⁺]

Example 36

N-([1-(4-Chlorophenyl)cyclopropyl]methyl)-2-(2,5-dioxoimidazolidin-4-yl)acetamide

^1H NMR (400MHz, DMSO- d_6): δ 10.53 (1H, d); 7.95 (1H, t); 7.73 (1H, s); 7.33-7.25 (4H, m); 4.18-4.15 (1H, m); 3.39-3.22 (2H, m); 2.54-2.37 (2H, m); 0.90-0.88 (2H, m); 0.76-0.73 (2H, m)

APCI-MS m/z : 322.3 [MH^+]

5

Example 37

N-2,3-Dihydro-1H-inden-2-yl-2-(2,5-dioxoimidazolidin-4-yl)acetamide

^1H NMR (400MHz, DMSO- d_6): δ 10.54 (1H, d); 8.24 (1H, d); 7.82 (1H, s); 7.22-7.20 (2H, m); 7.16-7.13 (2H, m); 4.47-4.42 (1H, m); 4.22-4.19 (1H, m); 3.19-3.12 (2H, m); 2.80-2.72 (2H, m); 2.54-2.36 (2H, m)

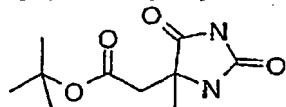
10

APCI-MS m/z : 274.2 [MH^+]

B. General procedure for preparation of (4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamides

15

I. tert-butyl(4-methyl-2,5-dioxoimidazolidin-4-yl)acetate

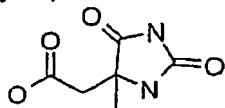


Tert-butyl acetoacetate (200mg; 1.3mmol), KCN (165mg; 2.5mmol) and $(\text{NH}_4)_2\text{CO}_3$ (605mg; 6.3mmol) was suspended in EtOH (2mL) and H_2O (2mL) in a sealed tube.

The mixture was heated to 85-90 °C and a solution was obtained, the heating was continued over night. The resulting slightly yellow solution was allowed to cool to room temperature and a precipitate was formed. The mixture was neutralised with 5% NaHSO_4 (aq) and diluted with H_2O (30mL). The slurry was extracted with EtOAc (2x50 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to give the title compound as a colourless solid. Obtained 210 mg (73% yield).

25

^1H -NMR(DMSO- D_6): δ 10.58 (1H, s), 7.91 (1H, s), 2.76+2.39 (1H each, ABq), 1.35 (9H, s), 1.23 (3H, s) ppm.

II. (4-methyl-2,5-dioxoimidazolidin-4-yl)-acetic acid

Deprotection afforded the title compound.

5

The following (4-methyl-2,5-dioxoimidazolidin-4-yl)acetamides were prepared by coupling of the appropriate amine to (4-methyl-2,5-dioxoimidazolidin-4-yl)-acetic acid by the general procedure A above.

Example 38

N-[2-(4-Chlorophenyl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide

¹H NMR (400MHz,DMSO-d₆): δ 10.42(1H, s); 7.94(1H, t); 7.35(1H, s); 7.35-7.31 (2H, m); 7.24-7.21 (2H, m); 3.21 (2H, q); 2.67 (2H, dd); 2.53-2.36 (2H, m); 1.21 (3H, s)

APCI-MS m/z: 310.3 [MH⁺]

15

Example 39

N-[2-(4-Chlorophenyl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide

¹H NMR (400MHz,DMSO-d₆): δ 10.42 (1H,m); 7.89-7.86 (1H, m); 7.65-7.64 (1H, m); 7.35-7.32 (2H, m); 7.24-7.22 (2H, m); 3.19-3.09 (2H, m); 2.87-2.77 (1H, m); 2.53-2.37

(2H, m); 1.19 (3H, d); 1.14 (3H, d)

APCI-MS m/z: 324.4 [MH⁺]

20

Example 40

N-[2-(4'-Cyano-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide

APCI-MS m/z: 377.3 [MH⁺]

25

Example 41

N-[2-(4'-Fluoro-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide

¹H NMR (400MHz, DMSO-d₆): δ 10.42 (1H, s); 7.99 (1H, t); 7.97-7.65 (3H, m); 7.56 (2H, d); 7.30-7.24 (4H, m); 3.28-3.23 (2H, m); 2.73-2.70 (2H, m); 2.54-2.39 (2H, m); 1.22 (3H, s)

APCI-MS m/z: 370.4 [MH⁺]

Example 42

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-fluoro-1,1'-biphenyl-4-yl)propyl]-acetamide

a) 2-(4-Bromo-phenyl)-propylamine

2-Phenyl-propylamine (1g, 7.4mmol) was dissolved in n-hexane (30mL) and HBr/aq (5 drops) together with ZnBr on silica (1.75mmol/g, 1g). Br₂ (14.8 mmol, 900μL) was slowly added and the slurry was stirred over night. The slurry was diluted with ethyl acetate (300mL) and washed with 2M Na₂CO₃ (300mL). The organic phase was dried over Na₂SO₄, filtered and evaporated to dryness. Purification and separation of regioisomers was done on semi prep-HPLC C₁₈-column (H₂O:CH₃CN, 1% NH₄OAc buffer, gradient 10% to 60% CH₃CN, 30 min). Yield 23%

b) [2-(4-Bromo-phenyl)-propyl]-carbamic acid tert-butyl ester

2-(4-Bromo-phenyl)-propylamine (18.7 mmol, 4g) was dissolved in 50mL THF (dry, mol sieves) and di-tert-butyl dicarbonate (1.2eq 23mmol 5g) was added slowly. The reaction mixture was stirred at room temperature for 1 hour before it was diluted with 300mL ethyl acetate and washed with 300mL sat. NaHCO₃/aq. The organic phase was dried over Na₂SO₄, filtrated and evaporated to dryness.

c) [2-(4'-Fluoro-biphenyl-4-yl)-propyl]-carbamic acid tert-butyl ester

The BOC-protected amine obtained in b) above was dissolved in a mixture of 10mL toluene, 2.5mL ethanol and 2.5mL 2M Na₂CO₃/aq. PdCl₂(dppf) (0.03eq, 50mg) and 4-fluorobenzeneboronic acid (1.05eq, 2.1mmol) were added. The solution was degassed with nitrogen and the vessel was sealed before it was stirred overnight at 80°C. The reaction mixture was diluted with 50mL toluene and 50mL water. After mixing, the organic layer was transferred directly on to a silica column and purified by chromatography (toluene- ethyl acetate).

d) 2-(4'-Fluoro-biphenyl-4-yl)-propylamine

To remove the protecting group the compound obtained in c) above was stirred in a mixture of 5mL conc. HCl in 10mL THF for 30 min. The solution was neutralised with 1M NaOH/aq and extracted with dichloromethane (2x). The combined organic layers was dried over Na₂SO₄, filtrated and evaporated to dryness.

e) 2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-fluoro-1,1'-biphenyl-4-yl)propyl]-acetamide

600µL of a 0.15M solution in NMP of 5-hydantoin acetic acid was mixed with 98mg of polystyrene-bound carbodiimide resin (loading 1.28mmol/g). 340µL of a 0.3M solution of HOBT in NMP was added to the mixture and vortexed for 10 minutes before 200µL of a 0.3M solution in NMP of 2-(4'-fluoro-biphenyl-4-yl)-propylamine was added. The reaction mixture was vortexed overnight at room temperature in a sealed vessel. Resin was removed by filtration and the solution was evaporated to dryness. The product was purified on semi prep-HPLC C₁₈-column (H₂O:CH₃CN, 0.1% TFA buffer, gradient 10% to 95% CH₃CN, 10 min).

¹H NMR (400MHz,DMSO-d₆): δ 10.55 (s, 1H), 8.00 (s, 1H), 7.76 (s, 1H), 7.68 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.32 - 7.25 (m, 4H), 4.22 - 4.17 (m, 1H), 3.23 (dd, *J* = 20.7, 6.3 Hz, 2H), 2.92 (q, *J* = 7.0 Hz, 1H), 2.57 - 2.35 (m, 2H), 1.21 (d, *J* = 7.1 Hz, 3H).

APCI-MS *m/z*: 370.2 [MH⁺]

The following compounds were prepared according to methods analogous to Example 42 above.

5 **Example 43**

N-[(1*S*,2*R*)-2-(4'-Methoxybiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

¹H NMR (400MHz,DMSO-d₆): δ 10.44 (d, *J* = 7.6 Hz, 1H), 8.18 (dd, *J* = 6.8, 4.3 Hz, 1H), 7.73 (s, 1H), 7.54 (d, *J* = 8.9 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.13 (dd, *J* = 8.3, 2.8 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 3.77 (s, 3H), 2.79 - 2.73 (m, 1H), 2.56 - 2.46 (m, 1H), 2.37 (d, *J* = 15.2 Hz, 1H), 1.90 (dt, *J* = 6.1, 3.1 Hz, 1H), 1.23 (s, 3H), 1.17 - 1.09 (m, 2H).
APCI-MS *m/z*: 394.3 [MH⁺]

Example 44

15 *N*-[(1*S*,2*R*)-2-(4'-Cyanobiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS *m/z*: 389.3 [MH⁺]

Example 45

20 *N*-[(1*S*,2*R*)-2-(4'-Acetylbiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

¹H NMR (400MHz,DMSO-d₆): δ 10.44 (d, *J* = 8.3 Hz, 1H), 8.20 (dd, *J* = 7.3, 4.3 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.73 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.21 (dd, *J* = 8.3, 3.1 Hz, 2H), 2.80 (dd, *J* = 7.4, 4.0 Hz, 1H), 2.59 (s, 3H), 2.56 - 2.35 (m, 2H), 1.95 (tq, *J* = 6.2, 3.2 Hz, 1H), 1.23 (s, 3H), 1.22 - 1.13 (m, 2H).

25 APCI-MS *m/z*: 406.3 [MH⁺]

Example 46

N-{[(1*S*,2*R*)-2-[4'-(Acetylamino)biphenyl-4-yl]cyclopropyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS *m/z*: 421.3 [*MH*⁺]

5

Example 47

N-[2-(4'-Cyanobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

¹H NMR (400MHz,DMSO-d₆): δ 10.43 (s, 1H), 7.95 - 7.85 (m, 5H), 7.67 (dd, *J* = 14.2, 8.5 Hz, 3H), 7.36 (dd, *J* = 8.3, 1.7 Hz, 2H), 1.19 (s, 3H), 1.21 (d, *J* = 3.9 Hz, 3H), 3.20 (sextet, *J* = 6.8 Hz, 2H), 2.94 - 2.87 (m, H), 2.54 - 2.39 (m, 2H).

APCI-MS *m/z*: 391.3 [*MH*⁺]

Example 48

15 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methoxybiphenyl-4-yl)ethyl]-acetamide

¹H NMR (400MHz,DMSO-d₆): δ 10.56 (s, 1H), 8.07 (t, *J* = 5.5 Hz, 1H), 7.80 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.24 - 4.20 (m, 1H), 3.82 (s, 3H), 3.34 - 3.26 (m, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.57 - 2.37 (m, 2H).

20 APCI-MS *m/z*: 368.2 [*MH*⁺]

Example 49

N-[2-(4'-Cyano-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

25 ¹H NMR (400MHz,DMSO-d₆): δ 10.41 (s, 1H), 7.92 (t, *J* = 5.6 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.77 (s, 1H), 7.69 - 7.62 (m, 4H), 7.34 (dd, *J* = 8.3, 1.7 Hz, 2H), 3.18 (t, *J* = 6.5 Hz, 2H), 2.89 (dd, *J* = 6.9, 2.6 Hz, 1H), 1.18 (s, 3H), 1.20 (d, *J* = 4.1 Hz, 3H), 2.53 (s, 3H), 2.51 - 2.38 (m, 2H).

APCI-MS *m/z*: 405.3 [*MH*⁺]

Example 50

2-(2,5-Dioxoimidazolidin-4-yl)-N-methyl-N-(2-phenylethyl)-acetamide

APCI-MS m/z: 276.2 [MH⁺]

5

Example 51

N-[1-(4-Chlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 296.1 [MH⁺]

10 **Example 52**

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-hydroxy-1-methyl-2-phenylethyl)-acetamide

APCI-MS m/z: 292.3 [MH⁺]

Example 53

15 N-{2-[4-(1,3-Benzodioxol-5-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 396.5 [MH⁺]

Example 54

20 2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(3'-methoxybiphenyl-4-yl)propyl]-acetamide

APCI-MS m/z: 382.4 [MH⁺]

Example 55

N-{2-[3'-(Acetylamino)biphenyl-4-yl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-
25 acetamide

APCI-MS m/z: 409.5 [MH⁺]

Example 56

N-[2-(3'-Acetylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 394.4 [MH⁺]

Example 57

N-[2-(4'-Acetylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

5 APCI-MS m/z: 394.5 [MH⁺]

Example 58

N-{2-[4-(1-Benzothien-2-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 408.4 [MH⁺]

10

Example 59

N-[2-(3'-Cyanobiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 377.4 [MH⁺]

15 **Example 60**

N-[2-(4'-Cyanobiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 377.4 [MH⁺]

Example 61

20 2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-fluoro-3'-methylbiphenyl-4-yl)propyl]-
acetamide

APCI-MS m/z: 384.4 [MH⁺]

Example 62

25 2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[3'-(methylthio)biphenyl-4-yl]propyl}-acetamide

APCI-MS m/z: 398.4 [MH⁺]

Example 63

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(6-methoxypyridin-3-yl)phenyl]propyl}-acetamide

APCI-MS m/z: 383.4 [MH⁺]

5

Example 64

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-methoxy-3'-methylbiphenyl-4-yl)propyl]-acetamide

APCI-MS m/z: 396.5 [MH⁺]

10

Example 65

N-{2-[4-(2,3-Dihydro-1-benzofuran-5-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 394.5 [MH⁺]

15

Example 66

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[3'-(trifluoromethoxy)biphenyl-4-yl]propyl}-acetamide

APCI-MS m/z: 436.5 [MH⁺]

20

Example 67

N-[2-(3',4'-Dimethoxybiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 412.5 [MH⁺]

25

Example 68

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-quinolin-3-ylphenyl)propyl]-acetamide

APCI-MS m/z: 403.5 [MH⁺]

Example 69

N-[2-(4'-Cyano-3'-methylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 391.5 [MH⁺]

5

Example 70

N-[5-(1,3-Benzodioxol-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 394.4 [MH⁺]

10

Example 71

2-(2,5-Dioxoimidazolidin-4-yl)-N-[5-(3-methoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide

APCI-MS m/z: 380.4 [MH⁺]

15

Example 72

N-[5-[3-(Acetylamino)phenyl]-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 407.5 [MH⁺]

20

Example 73

N-[5-(3-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 392.4 [MH⁺]

25

Example 74

N-[5-(4-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 392.5 [MH⁺]

Example 75

N-[5-(1-Benzothien-2-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

5 APCI-MS m/z: 406.4 [MH⁺]

Example 76

N-[5-(3-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

10 APCI-MS m/z: 375.4 [MH⁺]

Example 77

N-[5-(4-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

15 APCI-MS m/z: 375.4 [MH⁺]

Example 78

2-(2,5-Dioxoimidazolidin-4-yl)-N-[5-(4-fluoro-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide

20 APCI-MS m/z: 382.4 [MH⁺]

Example 79

2-(2,5-Dioxoimidazolidin-4-yl)-N-{5-[3-(methylthio)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide

25 APCI-MS m/z: 396.4 [MH⁺]

Example 80

2-(2,5-Dioxoimidazolidin-4-yl)-N-[5-(6-methoxypyridin-3-yl)-2,3-dihydro-1H-inden-2-yl]-acetamide

APCI-MS m/z: 381.4 [MH⁺]

Example 81

2-(2,5-Dioxoimidazolidin-4-yl)-N-[5-(4-methoxy-3-methylphenyl)-2,3-dihydro-1H-
inden-2-yl]-acetamide

APCI-MS m/z: 394.5 [MH⁺]

Example 82

N-[5-(2,3-Dihydro-1-benzofuran-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-
dioxoimidazolidin-4-yl)acetamide

APCI-MS m/z: 392.4 [MH⁺]

Example 83

N-[5-(3,4-Dimethoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-
yl)-acetamide

APCI-MS m/z: 410.5 [MH⁺]

Example 84

N-[2-(4'-Fluorobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-
acetamide

APCI-MS m/z: 384.5 [MH⁺]

Example 85

N-{2-[4-(1,3-Benzodioxol-5-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-
yl)-acetamide

APCI-MS m/z: 410.5 [MH⁺]

Example 86

N-[2-(3'-Methoxybiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 396.5 [MH⁺]

5

Example 87

N-{2-[4-(1-Benzothien-2-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 422.5 [MH⁺]

10

Example 88

N-[2-(3'-Cyanobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 391.5 [MH⁺]

15

Example 89

N-[2-(4'-Fluoro-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 398.5 [MH⁺]

20

Example 90

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-N-{2-[3'-(methylthio)biphenyl-4-yl]propyl}-acetamide

APCI-MS m/z: 412.5 [MH⁺]

25

Example 91

N-{2-[4-(6-Methoxypyridin-3-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 397.5 [MH⁺]

Example 92

N-[2-(4'-Methoxy-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

5 APCI-MS m/z: 410.5 [MH⁺]

Example 93

N-{2-[4-(2,3-Dihydro-1-benzofuran-5-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

10 APCI-MS m/z: 408.5 [MH⁺]

Example 94

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-N-{2-[3'-(trifluoromethoxy)biphenyl-4-yl]propyl}-acetamide

15 APCI-MS m/z: 450.5 [MH⁺]

Example 95

N-[2-(3',4'-Dimethoxybiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

20 APCI-MS m/z: 426.5 [MH⁺]

Example 96

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-N-[2-(4-quinolin-3-ylphenyl)propyl]-acetamide

25 APCI-MS m/z: 417.5 [MH⁺]

Example 97

N-[5-(4-Fluorophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 382.5 [MH⁺]

Example 98

N-[5-(1,3-Benzodioxol-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 408.5 [MH⁺]

Example 99

N-[5-(3-Methoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 394.5 [MH⁺]

Example 100

N-{5-[3-(Acetylamino)phenyl]-2,3-dihydro-1H-inden-2-yl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 421.5 [MH⁺]

Example 101

N-[5-(3-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 406.5 [MH⁺]

Example 102

N-[5-(4-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 406.5 [MH⁺]

Example 103

N-[5-(1-Benzothien-2-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 420.5 [MH⁺]

5

Example 104

N-[5-(3-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 389.5 [MH⁺]

10

Example 105

N-[5-(4-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 389.5 [MH⁺]

15

Example 106

N-[5-(4-Fluoro-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 396.5 [MH⁺]

20

Example 107

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-N-{5-[3-(methylthio)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide

APCI-MS m/z: 410.5 [MH⁺]

25

Example 108

N-[5-(6-Methoxypyridin-3-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

APCI-MS m/z: 395.5 [MH⁺]

Example 109

N-[5-(4-Methoxy-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

5 APCI-MS m/z: 408.5 [MH⁺]

Example 110

N-[5-(2,3-Dihydro-1-benzofuran-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

10 APCI-MS m/z: 406.5 [MH⁺]

Example 111

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-N-{5-[3-(trifluoromethoxy)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide

15 APCI-MS m/z: 448.5 [MH⁺]

Example 112

N-[5-(3,4-Dimethoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

20 APCI-MS m/z: 424.5 [MH⁺]

Example 113

N-[5-(4-Cyano-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide

25 APCI-MS m/z: 403.5 [MH⁺]

Example 114

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-{4-[4 (trifluoromethyl)phenoxy]phenyl}ethyl)-acetamide

a) **[2-(4-Hydroxy-phenyl)-ethyl]-carbamic acid tert-butyl ester**

2-(4-Hydroxyphenyl)-ethylamine (36.5mmol, 5g) was dissolved in 100mL THF (dry, mol
sieves) and di-tert-butyl dicarbonate (1.2eq 43.8mmol, 9.5g) was added slowly. The
5 reaction mixture was stirred at room temperature for 1 hour before it was diluted with
700mL ethyl acetate and washed with 500mL sat. NaHCO₃/aq. The organic phase was
dried over Na₂SO₄, filtrated and evaporated to dryness.

b) **{2-[4-(4-Trifluoromethyl-phenoxy)-phenyl]-ethyl}-carbamic acid tert-butyl ester**

10 0.5mmol of the BOC-protected amine obtained in a) above was dissolved in
dichloromethane (5mL) together with copper(II)acetate (0.5mmol, 90mg), powdered 4Å
mol sieves (app. 100mg) and 4-(trifluoromethyl)benzeneboronic acid (1mmol). After
stirring the reaction mixture overnight at room temperature the slurry was filtered and
purified by flash chromatography.

15 c) **2-[4-(4-Trifluoromethyl-phenoxy)-phenyl]-ethylamine**

The BOC-group was removed by stirring the compound obtained in b) above in
hydrochloric acid/THF (0.5mL conc. HCl /1.5mL THF) for 2 hours at room temperature
before it was made basic by adding 10.5mL 1M NaOH/aq. The free amine was extracted
20 with 3x10mL dichloromethane that was dried over Na₂SO₄, filtrated and evaporated to
dryness. Yield 0.32 mmol (62%).

d) **2-(2,5-Dioximidazolidin-4-yl)-N-(2-{4-[4 (trifluoromethyl)phenoxy]-
phenyl}ethyl)-acetamide**

25 The title compound was prepared by a method analogous to that described in Example
42e).

¹H NMR (400MHz, DMSO-d₆): δ 10.55 (s, 1H), 8.05 (t, *J* = 5.6 Hz, 1H), 7.79 (s, 1H), 7.72
(d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.08 (dd, *J* = 20.1, 8.5 Hz, 4H), 4.20 (dd, *J* =
6.2, 4.8 Hz, 1H), 3.29 (q, *J* = 6.8 Hz, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.57 - 2.36 (m, 2H).

APCI-MS m/z: 422.3 [MH⁺]

The following compounds were prepared according to methods analogous to Example 114 above.

5

Example 115

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(4-methoxyphenoxy)phenyl]ethyl}-acetamide

¹H NMR (400MHz,DMSO-d₆): δ 10.54 (s, 1H), 8.01 (t, *J* = 5.5 Hz, 1H), 7.77 (s, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.97 - 6.91 (m, 4H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.18 (dd, *J* = 6.2, 4.6
10 Hz, 1H), 3.72 (s, 3H), 3.22 (q, *J* = 6.8 Hz, 2H), 2.65 (t, *J* = 7.4 Hz, 2H), 2.55 - 2.33 (m, 2H).

APCI-MS m/z: 384.3 [MH⁺]

Example 116

15 **2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-{4-[4-(trifluoromethoxy)phenoxy]phenyl}ethyl)-acetamide**

¹H NMR (400MHz,DMSO-d₆): δ 10.55 (s, 1H), 8.04 (t, *J* = 5.5 Hz, 1H), 7.79 (s, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.07 (td, *J* = 6.4, 4.0 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 4.20 (dd, *J* = 6.1, 4.7 Hz, 1H), 3.27 (q, *J* = 6.8 Hz, 2H), 2.71 (t, *J* = 7.4 Hz, 2H),
20 2.57 - 2.35 (m, 2H).

APCI-MS m/z: 438.3 [MH⁺]

Example 117

N-{2-[4-(4-Chlorophenoxy)phenyl]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

25 ¹H NMR (400MHz,DMSO-d₆): δ 10.55 (s, 1H), 8.04 (t, *J* = 5.5 Hz, 1H), 7.79 (s, 1H), 7.41 (dd, *J* = 12.4, 3.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.01 - 6.95 (m, 4H), 4.20 (dd, *J* = 6.1, 4.7 Hz, 1H), 3.26 (q, *J* = 6.8 Hz, 2H), 2.70 (t, *J* = 7.4 Hz, 2H), 2.57 - 2.34 (m, 2H).

APCI-MS m/z: 388.3 [MH⁺]

Example 118

N-{2-[4-(4-Acetylphenoxy)phenyl]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

¹H NMR (400MHz,DMSO-d₆): δ 10.55 (s, 1H), 8.05 (t, J = 5.7 Hz, 1H), 7.97 (d, J = 8.9 Hz, 2H), 7.80 (s, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.04 (t, J = 8.8 Hz, 4H), 4.22 - 4.19 (m, 1H), 3.33 - 3.24 (m, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.58 - 2.35 (m, 5H).

APCI-MS m/z: 396.3 [MH⁺]

Example 119

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(pyridin-3-yloxy)phenyl]ethyl}-acetamide

APCI-MS m/z: 355.3 [MH⁺]

Example 120

2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-{4-[(6-methoxypyridin-3-yl)oxy]phenyl}ethyl)-acetamide

APCI-MS m/z: 385.1 [MH⁺]

Example 121

N-{2-[4-(4-Cyanophenoxy)phenyl]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

¹H NMR (400MHz,DMSO-d₆): δ 10.57 (s, 1H), 8.05 (t, J = 5.5 Hz, 1H), 7.81 (d, J = 8.9 Hz, 2H), 7.79 (s, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.8 Hz, 4H), 4.20 (dd, J = 6.1, 4.8 Hz, 1H), 3.28 (q, J = 6.7 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H), 2.56 - 2.36 (m, 2H).

APCI-MS m/z: 379.3 [MH⁺]

Example 122

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(4-methylphenoxy)phenyl]ethyl}-acetamide

¹H NMR (400MHz,DMSO-d₆): δ 10.55 (s, 1H), 8.03 (t, J = 5.5 Hz, 1H), 7.79 (s, 1H), 7.21 - 7.16 (m, 4H), 6.89 (d, J = 8.2 Hz, 4H), 4.20 (dd, J = 6.0, 4.5 Hz, 1H), 3.25 (q, J = 6.8 Hz, 2H), 2.68 (t, J = 7.4 Hz, 2H), 2.56 - 2.35 (m, 2H), 2.28 (s, 3H).

APCI-MS m/z: 368.3 [MH⁺]

Example 123

2-(2,5-Dioxoimidazolidin-4-yl)-N-{2-[4-(4-fluorophenoxy)phenyl]ethyl}-acetamide

¹H NMR (400MHz, DMSO-d₆): δ 10.53 (s, 1H), 8.02 (t, *J* = 5.5 Hz, 1H), 7.77 (s, 1H), 7.23
5 - 7.17 (m, 4H), 7.02 (tt, *J* = 4.5, 2.3 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.18 (dd, *J* = 6.0,
4.7 Hz, 1H), 3.24 (q, *J* = 6.8 Hz, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.54 - 2.33 (m, 2H).
APCI-MS *m/z*: 372.3 [MH⁺]

Example 124

10 **N-(2-Biphenyl-4-yl-2-hydroxy-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide**

a) 4-Phenylphenyloxirane

4-Phenyl-(α-bromoacetophenone), 8.25 g (0.030 mol), was slurried in methanol (150 mL).
Sodium borohydride (3.80 g; 0.10 mol) was added in portions to give an exothermal
15 reaction and a homogeneous reaction mixture. After 20 hours, water (600 mL) was added
and the mixture was extracted with dichloromethane (500 mL). The organic phase was
evaporated to give 7.25 g of crude product. NMR analysis showed mainly a 1:1 mixture of
epoxide and vicinal bromo alcohol.

20 **b) 2-Amino-1-biphenyl-4-yl-ethanol**

The product mixture obtained in a) above was dissolved in THF (ca 100 mL) and a large
excess of concentrated ammonia and ethanol was added to give a homogeneous system.
TLC analysis after 4 hours showed only starting materials. A slight increase in
temperature gave scarce improvement and the mixture was finally heated to 70° C in a
25 sealed vessel for 20 hours. TLC analysis showed absence of starting materials and NMR
analysis showed a complex mixture of products. The solvents were evaporated and
dichloromethane (150 mL) was added to give a precipitate. The mixture was filtered and
the solid, about 3.8 g, and filtrate was analysed with TLC and NMR. Analyses showed
mixtures of products but with, possibly, expected product in the solid phase. A sample of

the solid (1.04 g) was purified by silica gel chromatography (200 mL) using dichloromethane/ methanol/ concentrated ammonia (90 +10+1) as eluant. Evaporation of pure fractions gave 0.62 g of the sub-titled compound.

5 c) **N-(2-Biphenyl-4-yl-2-hydroxy-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide**

The title compound was prepared by a method analogous to that described in Example 42e).

¹H NMR (400MHz,DMSO-d₆): δ 10.57 (s, 1H), 8.10 (q, *J* = 5.8 Hz, 1H), 7.79 (s, 1H), 7.64 (t, *J* = 8.5 Hz, 4H), 7.45 (q, *J* = 7.7 Hz, 4H), 7.35 (t, *J* = 7.3 Hz, 1H), 5.49 (s, 1H), 4.66 (t, 10 *J* = 3.7 Hz, 1H), 4.26 - 4.17 (m, 1H), 3.20 - 3.09 (m, 1H), 2.59 (dt, *J* = 15.5, 3.5 Hz, 1H), 2.52 - 2.39 (m, 2H).

APCI-MS *m/z*: 336.3 [MH⁺]

Example 125

15 **N-[2-(1,1'-Biphenyl-4-yl)-2-methoxyethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide**

a) 4-(2-Amino-1-methoxyethyl)-biphenyl

4-Vinyl-biphenyl, 1.70 g (9.4 mmol), was dissolved in methanol (10 mL) and dichloromethane (15 mL). Bromine, 0.48 mL (9.4 mmol), dissolved in methanol (10 mL) was added over 30 minutes and TLC analysis showed complete reaction. The mixture was diluted with dichloromethane and added to an aqueous solution of sodium hydrogen sulphite and the mixture was shaken. The dichloromethane phase was washed with aqueous sodium hydrogen carbonate and water and evaporated to give 2.81g product. The product was purified by silica gel chromatography silica gel (200 mL) with heptane/ ethyl acetate (95 + 5) to give 1.00 g (39 %) of pure 4-(2-bromo-1-methoxy-ethyl)-biphenyl. 25 4-(2-Bromo-1-methoxyethyl)-biphenyl, 1.00 g (3.64 mmol), was dissolved in ethanol (20 mL) and added to a large excess of concentrated ammonia (20 mL). The mixture was heated to 100° C in a sealed vessel for 16 hours and evaporated. Chromatography on silica

gel (180 mL) with dichloromethane followed by dichloromethane/ methanol/ concentrated ammonia (90 + 10 + 1) gave 0.47 g (61 %) of the sub-titled compound.

5 **b) N-[2-(1,1'-Biphenyl-4-yl)-2-methoxyethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide**

The title compound was prepared by a method analogous to that described in Example 42e).

¹H NMR (400MHz,DMSO-d₆): δ 10.56 (s, 1H), 8.16 (d, *J* = 5.5 Hz, 1H), 7.78 (d, *J* = 6.2 Hz, 1H), 7.70 - 7.64 (m, 4H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.42 - 7.34 (m, 3H), 4.29 (dt, *J* = 10 7.8, 5.0 Hz, 1H), 4.23 - 4.19 (m, 1H), 3.19 (s, 3H), 2.61 - 2.53 (m, 2H), 2.50 - 2.39 (m, 2H).

APCI-MS *m/z*: 368.2 [MH⁺]

Example 126

15 **N-[2-(1,1'-Biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-N-methylacetamide**

a) (4-Phenylphenethyl)-N-methylamine

4-Phenylphenethyl amine, 0.48 g (2.4 mmol), was added to an excess of methyl formate (5 mL) and dichloromethane (5 mL) was added to improve solubility. The heterogeneous
20 reaction mixture was refluxed to give a solution within 20 hours. NMR analysis of a sample showed almost complete conversion to N-formyl amine. The reaction mixture was evaporated to give 0.47 g (87%). The formyl compound, 0.47 g (2.09 mmol), was dissolved in THF and 2.1 mL of 1.0 M lithium aluminium hydride (2.1 mmol) in THF was added. TLC analysis after 20 hours showed only starting material and 2 mL (2 mmol) of
25 lithium aluminium hydride solution was added. Analysis after 1 hour showed starting material and the mixture was heated to reflux. After 1.5 hours a precipitate was formed, the starting material consumed and tetrahydrofuran (15 ml) was added. The mixture was quenched by successive addition of water (0.15 g), 15 % aqueous sodium hydroxide (0.15 g) and water (0.45 g). The mixture was filtered and evaporated to give 0.33 g crude

product. The crude product was purified by silica gel chromatography (100 mL) using dichloromethane/ methanol/ concentrated ammonia (90 + 10 + 1) as eluant. Evaporation of pure fractions gave 78 mg (18 %) of the sub-titled compound.

5 **b) N-[2-(1,1'-Biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-N-methylacetamide**

The title compound was prepared by a method analogous to that described in Example 42e).

APCI-MS m/z: 352.3 [MH⁺]

10

Example 127

2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-phenylethynyl-piperidin-1-yl)ethyl]-acetamide

a) 4-(Phenylethynyl)piperidine

15 N-BOC-4-ethynylpiperidin, 0.5 g (2.40 mmol), and iodobenzene, 0.29 mL (2.64 mmol) were dissolved in triethylamine (9 mL) and argon was passed through for a few minutes. Copper(I) iodide, 0.087 g (0.5 mmol), and bis(triphenylphosphine)palladium dichloride, 0.070 g (0.1 mmol), were added and the mixture was heated to 82°C in a closed vessel for 17 hours. TLC analysis indicated complete reaction. Triethylamine was evaporated and
20 the mixture was purified by silica gel chromatography (75 mL) using heptane/ethyl acetate (4 + 1) as eluant. Evaporation of pure fractions gave 0.497 g (73 %) of N-BOC-4-(phenylethynyl)piperidine. The protected piperidine, 0.497 g (1.74 mmol), was dissolved in dichloromethane and trifluoroacetic acid (1 mL) was added. The reaction was completed within 20 hours and the mixture was evaporated to give an oil. NMR analysis
25 showed pure ammonium trifluoroacetate, contaminated with trifluoroacetic acid. The product was dissolved in dichloromethane and extracted with aqueous sodium hydrogen carbonate and water. Evaporation of solvent gave 0.284 g (88 %) of the sub-titled compound.

b) 2-[4-(Phenylethynyl)piperidin-1-yl]ethanamine

4-(Phenylethynyl)piperidine (0.5 mmol, 92mg) was dissolved in acetonitrile (anhydrous 4Å, 4mL) together with bromoethylphtalimide (0.5mmol, 128mg) and K₂CO₃ (2mmol, 276mg). The reaction mixture was heated to reflux for 3hours, diluted with ethyl acetate (50mL) and washed with HCl/aq (1M, 50mL). The organic phase was dried over Na₂SO₄, filtered and evaporated to dryness. The protection group was removed by stirring the compound in methylamine (33% in ethanol, 5mL) for another 3 hours. The mixture was evaporated, diluted with ethyl acetate (50mL) and washed with NaOH (1M, 50mL). The organic phase was dried over Na₂SO₄, filtered and evaporated to dryness. The crude product was used without further purification.

c) 2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4-phenylethynyl-piperidin-1-yl)ethyl]-acetamide

The title compound was prepared by a method analogous to that described in Example 42e).

¹H NMR (400MHz, CDCl₃): δ 9.96 (s, 1H), 9.67 (s, 1H), 8.23 (s, 1H), 7.34 (dd, *J* = 66.3, 28.1 Hz, 5H), 4.35 (s, 1H), 3.82 - 1.88 (m, 15H).

APCI-MS *m/z*: 369.3 [MH⁺]

Example 128***N*-{2-[(4-Bromobenzyl)oxy]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide****a) 2-(4-Bromo-benzyloxy)-ethylamine hydrochloride**

Sodium hydride (60 % in oil, 0.613 g, 15 mmol) was added in small portions over 5 minutes to a solution of tert-butyl N-(2-hydroxyethyl)-carbamate (1.771 g, 10.99 mmol), 4-bromobenzylbromide (2.676 g, 10.708 mmol) in dimethyl formamide (50 ml). The mixture was stirred for 2 hours at ambient temperature under argon. The mixture was partitioned between water (250 mL), ethyl acetate (50 mL) and heptane (50 mL). The organic phase was washed two times with water (30 mL). Evaporation afforded 3.13g of a

clear oil. The oil was stirred in 2.5 M HCl in ethyl acetate (50 mL) for 2 hours. Filtering and washing with ethyl acetate afforded the sub-titled compound (2.256 g, 98.1 % yield).
¹HNMR (300 MHz, DMSO-d₆): δ 8.16 (3H, bs); 7.55 (2H, d); 7.36 (2H, d); 4.51 (2H, s); 3.64 (2H, t); 2.99 (2H, t).

APCI-MS m/z: 229.9; 231.9 [MH⁺]

b) N-{2-[(4-bromobenzyl)oxy]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide

The title compound was prepared by a method analogous to that described in Example 42e).

¹HNMR (300 MHz, DMSO-d₆): δ 10.56 (1H, s); 8.08 (1H, t); 7.81 (1H, s); 7.54 (1H, d); 7.30 (1H, d); 4.45 (2H, s); 4.20 (1H, m); 3.25 (2H, q); 2.50 (2H, p); 2.50 (2H, m).

APCI-MS m/z: 370; 372 [MH⁺]

Example 129

2-(1,1'-Biphenyl-4-yl)-2-oxoethyl (2,5-dioxoimidazolidin-4-yl)acetate

Hydantoin acetic acid (109 mg, 0.69 mmol), 2-bromo-4'-phenylacetophenone (191 mg, 0.69 mmol) and N-ethyl-diisopropylamine (120 µl, 0.70 mmol) were stirred in dimethylformamide (5.0 mL) at 50°C for 3 hours. Evaporation and chromatography on silica (dichloromethane/methanol: 100/3) afforded 123 mg of the title compound in 50.1 % yield.

¹HNMR (300 MHz, DMSO-d₆): δ 10.68 (1H, s); 8.06 (2H, d); 7.90 (1H, s); 7.87 (2H, d); 7.77 (2H, d); 7.55-7.42 (3H, m); 5.55 (2H, d); 4.32 (1H, dt); 2.90 (2H, d).

APCI-MS m/z: 353.1 [MH⁺]

Pharmacological Example

Isolated Enzyme Assay

Recombinant human MMP12 catalytic domain may be expressed and purified as described by Parkar A.A. *et al*, (2000), Protein Expression and Purification, 20:152. The purified

enzyme can be used to monitor inhibitors of activity as follows: MMP12 (50 ng/ml final concentration) is incubated for 60 minutes at room temperature with the synthetic substrate Mac-Pro-Cha-Gly-Nva-His-Ala-Dpa-NH₂ in assay buffer (0.1M "Tris-HCl" (trade mark) buffer, pH 7.3 containing 0.1M NaCl, 20mM CaCl₂, 0.020 mM ZnCl and 0.05% (w/v) "Brij 35" (trade mark) detergent) in the presence (5 concentrations) or absence of inhibitors. Activity is determined by measuring the fluorescence at λ_{ex} 320nm and λ_{em} 405nm. Percent inhibition is calculated as follows: % Inhibition is equal to the $[\text{Fluorescence}_{plus\ inhibitor} - \text{Fluorescence}_{background}]$ divided by the $[\text{Fluorescence}_{minus\ inhibitor} - \text{Fluorescence}_{background}]$.

10

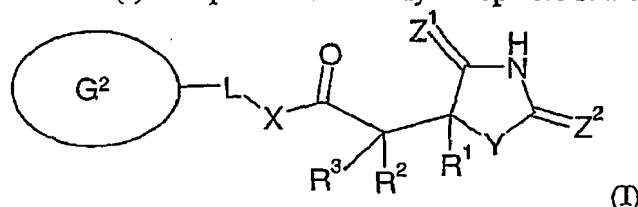
For example, the following table shows the IC₅₀ figures for a representative selection of compounds according to the invention when tested in the MMP12 enzyme assay.

Compound of Example No.	Human MMP12 IC ₅₀ (μm)
1	0.022
2	0.007
5	0.032
14	0.006
21	0.008
22	0.015
23	0.006
24	0.004
26	0.017
27	0.005

15

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof



5 wherein

X represents an oxygen atom or a group NR^4 or CH_2 ;

Y represents NH or N-methyl;

Z^1 and Z^2 each independently represent an oxygen or sulphur atom, provided that at least one of Z^1 and Z^2 represents an oxygen atom;

10 Either R^1 represents hydrogen or a group selected from C_1 - C_6 alkyl and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, carboxyl, $-\text{NR}^5\text{R}^6$, $-\text{CONR}^7\text{R}^8$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylcarbonyl(oxy),
 15 $-\text{S}(\text{O})_m\text{C}_1$ - C_6 alkyl where m is 0, 1 or 2, C_1 - C_6 alkylsulphonylamino, C_1 - C_6 alkoxy carbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo, carboxyl, cyano, C_1 - C_6 alkyl,
 20 C_1 - C_6 alkoxy carbonyl and C_1 - C_6 hydroxyalkyl,
 R^2 represents hydrogen or C_1 - C_6 alkyl, and
 R^3 represents hydrogen or C_1 - C_6 alkyl,

or

R^1 and R^2 together with the carbon atoms to which they are attached form a saturated
 25 5- to 6-membered ring optionally comprising a ring heteroatom selected from nitrogen, oxygen and sulphur, and R^3 is as defined above,

or

R^2 and R^3 together with the carbon atom to which they are attached form a saturated 5- to 6-membered ring optionally comprising a ring heteroatom selected from nitrogen, oxygen and sulphur, and R^1 is as defined above;

5 R^4 represents hydrogen or C_1 - C_6 alkyl;

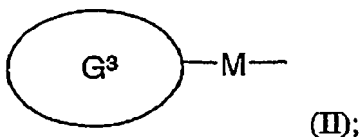
R^5 , R^6 , R^7 and R^8 each independently represent hydrogen or C_1 - C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy;

L represents $-CH_2C(O)-$ or $-C(O)CH_2-$, or

L represents a C_2 - C_6 alkyl or C_2 - C_6 alkynyl group optionally interrupted or
 10 terminated by at least one moiety selected from O, NH, S, SO, SO_2 and $C(O)$, or L represents a C_3 - C_6 cycloalkyl, methyl- C_3 - C_6 cycloalkyl or C_3 - C_6 cycloalkylmethyl group, each of the recited groups being optionally substituted with at least one substituent selected from hydroxyl, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy and C_1 - C_4 haloalkoxy, or

15 L represents a C_3 - C_4 alkylene chain, the ends of which are attached to adjacent ring carbon atoms in the 5- to 10-membered ring system of G^2 to form a ring;

G^2 represents a saturated or unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with at least one substituent selected from halogen,
 20 hydroxyl, cyano, nitro, C_1 - C_6 alkyl (optionally substituted by one or more of cyano, halogen, hydroxyl and methoxy), C_2 - C_6 alkenyl, C_1 - C_6 alkoxy (optionally substituted by one or more halogen atoms), $-S(O)_n C_1$ - C_6 alkyl where n is 0, 1 or 2, C_1 - C_6 alkylcarbonyl(amino), C_1 - C_6 alkylcarbonyloxy, phenyl, benzyloxy, $-NR^9 R^{10}$ and a group of formula



25 R^9 and R^{10} each independently represent hydrogen or C_1 - C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1 - C_6 alkoxy;

M represents a bond or -O-, -S-, -C≡C-, -CH₂O- or -OCH₂-;

G³ represents an unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, nitro, C₁-C₆ alkyl (optionally substituted by one or more of cyano, halogen, hydroxyl and methoxy), C₂-C₆ alkenyl, C₁-C₆ alkoxy (optionally substituted by one or more halogen atoms), -S(O)_tC₁-C₆ alkyl where t is 0, 1 or 2, C₁-C₆ alkylcarbonyl(amino), C₁-C₆ alkylcarbonyloxy, phenyl, benzyloxy and -NR¹¹R¹²; and

R¹¹ and R¹² each independently represent hydrogen or C₁-C₆ alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy.

2. A compound according to claim 1, wherein X represents a group NR⁴.
3. A compound according to claim 2, wherein R⁴ represents hydrogen.
4. A compound according to any one of claims 1 to 3, wherein Y represents NH.
5. A compound according to any one of the preceding claims, wherein Z¹ and Z² both represent an oxygen atom.
6. A compound according to any one of the preceding claims, wherein L represents a C₂-C₄ alkyl group optionally interrupted or terminated by one or two moieties independently selected from O, NH, S, SO, SO₂ and C(O), or L represents a C₃-C₆ cycloalkyl, methylC₃-C₆ cycloalkyl or C₃-C₆ cycloalkylmethyl group, each of the recited groups being optionally substituted with one or two substituents independently selected from hydroxyl, halogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy and C₁-C₄ haloalkoxy.

7. A compound according to any one of claims 1 to 5, wherein L represents a C₃-C₄ alkylene chain, the ends of which are attached to adjacent ring carbon atoms in the 5- to 10-membered ring system of G² to form a ring.

5 8. A compound according to claim 7, wherein the 5- to 10-membered ring system of G² is phenyl.

9. A compound according to any one of claims 1 to 7, wherein, in G², the saturated or unsaturated 5- to 10-membered ring system is selected from cyclopentyl, cyclohexyl,
10 bicyclo[2.2.1]heptyl, cyclopentenyl, cyclohexenyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazabicyclo[2.2.1]hept-2-yl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, quinolinyl, 2,3-dihydrobenzofuranyl, tetrahydropyranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, imidazolyl, pyrimidinyl,
15 benzimidazolyl, triazolyl, tetrazolyl and pyridinyl.

10. A compound according to any one of the preceding claims, wherein, in G³, the unsaturated 5- to 10-membered ring system is selected from cyclopentenyl, cyclohexenyl, phenyl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, quinolinyl, 2,3-
20 dihydrobenzofuranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, imidazolyl, pyrimidinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl.

11. A compound according to claim 1 which is selected from the group consisting of:
25 2-(2,5-Dioxoimidazolidin-4-yl)-N-[2-(4'-fluoro-biphenyl-4-yl)-ethyl]-acetamide,
N-[2-(4'-Cyano-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-N-(2-phenyl-cyclopropyl)-acetamide,
N-[2-(4-Chlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
N-(2-Biphenyl-4-yl-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

- 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(7-methyl-1H-indol-3-yl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-phenoxyphenyl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-fluorophenyl)ethyl]-acetamide,
N-[2-(4-Bromophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
5 *N*-[2-(2,4-Dichlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
N-[2-(3'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
N-[2-(4'-Benzyloxy-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-thiophen-3-yl-phenyl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-thiophen-2-yl-phenyl)ethyl]-acetamide,
10 *N*-[2-(4'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-methylsulfanyl-biphenyl-4-yl)ethyl]-
acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-nitro-biphenyl-4-yl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-methyl-biphenyl-4-yl)ethyl]-acetamide,
15 *N*-[2-(3'-Acetyl-amino-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-naphthalen-2-yl-phenyl)ethyl]-acetamide,
N-[2-(3',5'-Dichloro-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methyl-biphenyl-4-yl)ethyl]-acetamide,
N-[2-(4-Benzofuran-2-yl-phenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
20 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methoxy-biphenyl-4-yl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-[1,1';4',1'']terphenyl-4-ylethyl)-acetamide,
N-[2-(4'-Acetyl-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
N-[2-(4-Benzo[b]thiophen-2-yl-phenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-
acetamide,
25 *N*-[2-(4'-Cyanomethyl-biphenyl-4-yl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-pyridin-3-yl-phenyl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[4-(1H-pyrrol-2-yl)phenyl]ethyl}-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-furan-3-yl-phenyl)ethyl]-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-furan-2-yl-phenyl)ethyl]-acetamide,

- 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-thiophen-2-yl-ethyl)-acetamide,
N-[2-(4-tert-Butylphenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
N-[2-(4-Chlorophenyl)-1-methylethyl]-2-(2,5-dioxoimidazolidin-4-yl)acetamide,
N-{[1-(4-Chlorophenyl)cyclopropyl]methyl}-2-(2,5-dioxoimidazolidin-4-
5 yl)acetamide,
N-2,3-Dihydro-1H-inden-2-yl-2-(2,5-dioxoimidazolidin-4-yl)acetamide,
N-[2-(4-Chlorophenyl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide,
N-[2-(4-Chlorophenyl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide,
N-[2-(4'-Cyano-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-
10 yl)acetamide,
N-[2-(4'-Fluoro-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-
yl)acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-fluoro-1,1'-biphenyl-4-yl)propyl]-acetamide,
N-[(1*S*,2*R*)-2-(4'-Methoxybiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-
15 dioxoimidazolidin-4-yl)-acetamide,
N-[(1*S*,2*R*)-2-(4'-Cyanobiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-
dioxoimidazolidin-4-yl)-acetamide,
N-[(1*S*,2*R*)-2-(4'-Acetylbiphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-
dioxoimidazolidin-4-yl)-acetamide,
20 *N*-{[(1*S*,2*R*)-2-(4'-(Acetylamino)biphenyl-4-yl)cyclopropyl]-2-(4-methyl-2,5-
dioxoimidazolidin-4-yl)-acetamide,
N-[2-(4'-Cyanobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-
acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methoxybiphenyl-4-yl)ethyl]-acetamide,
25 *N*-[2-(4'-Cyano-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-
yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-methyl-*N*-(2-phenylethyl)-acetamide,
N-[1-(4-Chlorophenyl)ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,
2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-acetamide,

N-{2-[4-(1,3-Benzodioxol-5-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(3'-methoxybiphenyl-4-yl)propyl]-acetamide,

N-{2-[3'-(Acetylamino)biphenyl-4-yl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-
5 acetamide,

N-[2-(3'-Acetylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Acetylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{2-[4-(1-Benzothien-2-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-
acetamide,

10 *N*-[2-(3'-Cyanobiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Cyanobiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-fluoro-3'-methylbiphenyl-4-yl)propyl]-
acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[3'-(methylthio)biphenyl-4-yl]propyl}-
15 acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[4-(6-methoxypyridin-3-yl)phenyl]propyl}-
acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4'-methoxy-3'-methylbiphenyl-4-yl)propyl]-
acetamide,

20 *N*-{2-[4-(2,3-Dihydro-1-benzofuran-5-yl)phenyl]propyl}-2-(2,5-dioxoimidazolidin-4-yl)-
acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{2-[3'-(trifluoromethoxy)biphenyl-4-yl]propyl}-
acetamide,

N-[2-(3',4'-Dimethoxybiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-
25 acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-quinolin-3-ylphenyl)propyl]-acetamide,

N-[2-(4'-Cyano-3'-methylbiphenyl-4-yl)propyl]-2-(2,5-dioxoimidazolidin-4-yl)-
acetamide,

N-[5-(1,3-Benzodioxol-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(3-methoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

5 *N*-{5-[3-(Acetylamino)phenyl]-2,3-dihydro-1H-inden-2-yl}-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

10 *N*-[5-(4-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(1-Benzothien-2-yl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

15 *N*-[5-(4-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(4-fluoro-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

20 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-{5-[3-(methylthio)phenyl]-2,3-dihydro-1H-inden-2-yl}-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(6-methoxypyridin-3-yl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[5-(4-methoxy-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-acetamide,

N-[2-(4'-Fluorobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{2-[4-(1,3-Benzodioxol-5-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

5 *N*-[2-(3'-Methoxybiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-{2-[4-(1-Benzothien-2-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

10 *N*-[2-(3'-Cyanobiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Fluoro-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-{2-[3'-(methylthio)biphenyl-4-yl]propyl}-acetamide,

15 *N*-{2-[4-(6-Methoxypyridin-3-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(4'-Methoxy-3'-methylbiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

20 *N*-{2-[4-(2,3-Dihydro-1-benzofuran-5-yl)phenyl]propyl}-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-{2-[3'-(trifluoromethoxy)biphenyl-4-yl]propyl}-acetamide,

N-[2-(3',4'-Dimethoxybiphenyl-4-yl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

25 2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-[2-(4-quinolin-3-ylphenyl)propyl]-acetamide,

N-[5-(4-Fluorophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(1,3-Benzodioxol-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Methoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

5 *N*-[5-[3-(Acetylamino)phenyl]-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

10 *N*-[5-(4-Acetylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(1-Benzothien-2-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(3-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

15 *N*-[5-(4-Cyanophenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Fluoro-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

20 2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-[5-[3-(methylthio)phenyl]-2,3-dihydro-1H-inden-2-yl]-acetamide,

N-[5-(6-Methoxypyridin-3-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Methoxy-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

25 *N*-[5-(2,3-Dihydro-1-benzofuran-5-yl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(4-Methyl-2,5-dioxoimidazolidin-4-yl)-*N*-[5-[3-(trifluoromethoxy)phenyl]-2,3-dihydro-1H-inden-2-yl]-acetamide,

N-[5-(3,4-Dimethoxyphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[5-(4-Cyano-3-methylphenyl)-2,3-dihydro-1H-inden-2-yl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamide,

5 2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-{4-[4 (trifluoromethyl)phenoxy]phenyl}ethyl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-[4-(4-methoxyphenoxy)phenyl]ethyl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-{4-[4-(trifluoromethoxy)phenoxy]phenyl}ethyl)-
10 acetamide,

N-(2-[4-(4-Chlorophenoxy)phenyl]ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-(2-[4-(4-Acetylphenoxy)phenyl]ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-[4-(pyridin-3-yloxy)phenyl]ethyl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-{4-[(6-methoxypyridin-3-yl)oxy]phenyl}ethyl)-
15 acetamide,

N-(2-[4-(4-Cyanophenoxy)phenyl]ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-[4-(4-methylphenoxy)phenyl]ethyl)-acetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-(2-[4-(4-fluorophenoxy)phenyl]ethyl)-acetamide,

N-(2-Biphenyl-4-yl-2-hydroxy-ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

20 *N*-[2-(1,1'-Biphenyl-4-yl)-2-methoxyethyl]-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

N-[2-(1,1'-Biphenyl-4-yl)-ethyl]-2-(2,5-dioxoimidazolidin-4-yl)-*N*-methylacetamide,

2-(2,5-Dioxoimidazolidin-4-yl)-*N*-[2-(4-phenylethynyl-piperidin-1-yl)ethyl]-
acetamide,

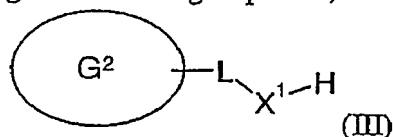
N-(2-[(4-Bromobenzyl)oxy]ethyl)-2-(2,5-dioxoimidazolidin-4-yl)-acetamide,

25 2-(1,1'-Biphenyl-4-yl)-2-oxoethyl (2,5-dioxoimidazolidin-4-yl)acetate,

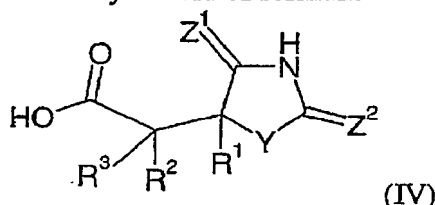
and pharmaceutically acceptable salts and solvates thereof.

12. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in claim 1 which comprises,

(a) when X represents an oxygen atom or a group NR^4 , reacting a compound of formula

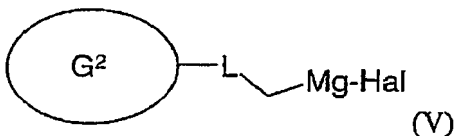


wherein X^1 represents an oxygen atom or a group NR^4 and L, G^2 and R^4 are as defined in formula (I), with an activated carboxylic acid of formula



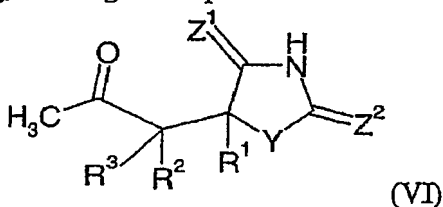
wherein Y, Z^1 , Z^2 , R^1 , R^2 and R^3 are as defined in formula (I); or

(b) when X represents CH_2 , reacting an activated carboxylic acid of formula (IV) as defined in (a) above with methoxymethylamine or a salt thereof followed by reaction with a Grignard reagent of formula

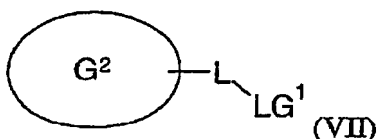


wherein Hal represents a halogen atom and L and G^2 are as defined in formula (I); or

(c) when X represents CH_2 , reacting a compound of formula



wherein Y, Z^1 , Z^2 , R^1 , R^2 and R^3 are as defined in formula (I), with a compound of formula



wherein LG^1 represents a leaving group and L and G^2 are as defined in formula (I) in the presence of a strong base;

and optionally after (a), (b) or (c) forming a pharmaceutically acceptable salt or solvate.

13. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 11 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

5

14. A process for the preparation of a pharmaceutical composition as claimed in claim 13 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in any one of claims 1 to 11 with a pharmaceutically acceptable adjuvant, diluent or carrier.

10

15. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 11 for use in therapy.

15

16. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 11 in the manufacture of a medicament for use in the treatment of an obstructive airways disease.

17. Use according to claim 16, wherein the obstructive airways disease is asthma or chronic obstructive pulmonary disease.

20

18. A method of treating a disease or condition mediated by MMP12 which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 11.

25

19. A method of treating an obstructive airways disease which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 11.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01328

A. CLASSIFICATION OF SUBJECT MATTER

C07D 233/78, A61K 31/4166, A61P 11/06, A61P 17/02, A61P 17/06, A61P 19/00,
 IPC7: A61P 25/28, A61P 29/00, A61P 35/00, A61P 37/00, A61P 41/00 // C07C 233/01, A61K 31/165
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, BIOSIS, EMBASE, MEDLINE, EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1191024 A1 (TSCHESCHE, HARALD), 27 March 2002 (27.03.02), see especially compounds 23-25 on page 5	1-19
	--	
X	WO 0035886 A2 (AXYS PHARMACEUTICALS, INC.), 22 June 2000 (22.06.00), pages 77 and 86, Ex. No. 383 in Table 2a, page 155, lines 12 and 19; claims	1-19
	--	
P,X	WO 0296426 A1 (ASTRAZENECA AB), 26 Sept 2002 (26.09.02), page 1 - page 10; page 183, pages 1-10, page 183, example 104, the claims	1-19
	--	

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

3 December 2003

Date of mailing of the international search report

05-12-2003

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01328

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02074750 A1 (ASTRAZENECA AB), 26 Sept 2002 (26.09.02) --	1-19
P,X	WO 02074749 A1 (ASTRAZENECA AB), 26 Sept 2002 (26.09.02) --	1-19
P,X	WO 02074752 A1 (ASTRAZENECA AB), 26 Sept 2002 (26.09.02) --	1-19
A	WO 0134573 A1 (PHARMACIA AB), 17 May 2001 (17.05.01) --	1-19
A	EP 0709375 A1 (ZENECA LIMITED), 1 May 1996 (01.05.96), abstract, page 21, claims -----	1-19

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/09/03

International application No.

PCT/SE 03/01328

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1191024 A1	27/03/02	NONE	
WO 0035886 A2	22/06/00	AU 2711500 A BR 9916363 A CA 2355249 A CN 1344256 T CZ 20012006 A EE 200100323 A EP 1140859 A HU 0104987 A IL 143801 D JP 2002532479 T NO 20012980 A PL 349192 A SK 7972001 A	03/07/00 11/12/01 22/06/00 10/04/02 13/03/02 15/08/02 10/10/01 29/07/02 00/00/00 02/10/02 01/08/01 01/07/02 04/06/02
WO 0296426 A1	26/09/02	NONE	
WO 02074767 A1	26/09/02	AU 5282101 A SE 0100902 D WO 02074748 A WO 02074750 A WO 02074751 A	26/11/01 00/00/00 26/09/02 26/09/02 26/09/02
WO 02074750 A1	26/09/02	AU 5282101 A SE 0100902 D WO 02074748 A WO 02074751 A WO 02074767 A AU 5282201 A SE 0100903 D WO 02074749 A WO 02074752 A	26/11/01 00/00/00 26/09/02 26/09/02 26/09/02 12/11/01 00/00/00 26/09/02 26/09/02
WO 02074749 A1	26/09/02	AU 5282201 A SE 0100903 D WO 02074750 A WO 02074752 A	12/11/01 00/00/00 26/09/02 26/09/02
WO 02074752 A1	26/09/02	AU 5282201 A SE 0100903 D WO 02074749 A WO 02074750 A	12/11/01 00/00/00 26/09/02 26/09/02
WO 0134573 A1	17/05/01	AU 1746401 A SE 9904044 D	06/06/01 00/00/00
EP 0709375 A1	01/05/96	GB 9421411 D JP 8208605 A US 5710169 A US 6147083 A GB 9512367 D	00/00/00 13/08/96 20/01/98 14/11/00 00/00/00

Form PCT/ISA/210 (patent family annex) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01328

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-19
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

INTERNATIONAL SEARCH REPORT

Int. application No.
PCT/SE03/01328

Claims 18-19 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claim. The search has been based on the alleged effects of the compounds/compositions.

Form PCT/ISA/210 (extra sheet) (July 1998)